REVIEW

Red Raspberries and Their Bioactive Polyphenols: Cardiometabolic and Neuronal Health Links[1,2]

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ABSTRACT

Diet is an essential factor that affects the risk of modern-day metabolic diseases, including cardiovascular disease, diabetes mellitus, obesity, and Alzheimer disease. The potential ability of certain foods and their bioactive compounds to reverse or prevent the progression of the pathogenic processes that underlie these diseases has attracted research attention. Red raspberries (*Rubus idaeus* L.) are unique berries with a rich history and nutrient and bioactive composition. They possess several essential micronutrients, dietary fibers, and polyphenolic components, especially ellagitannins and anthocyanins, the latter of which give them their distinctive red coloring. In vitro and in vivo studies have revealed various mechanisms through which anthocyanins and ellagitannins (via ellagic acid or their urolithin metabolites) and red raspberry extracts (or the entire fruit) could reduce the risk of or reverse metabolically associated pathophysiologies. To our knowledge, few studies in humans are available for evaluation. We review and summarize the available literature that assesses the health-promoting potential of red raspberries and select components in modulating metabolic disease risk, especially cardiovascular disease, diabetes mellitus, obesity, and Alzheimer disease—all of which share critical metabolic, oxidative, and inflammatory links. The body of research is growing and supports a potential role for red raspberries in reducing the risk of metabolically based chronic diseases. *Adv Nutr* 2016;7:44–65.

Keywords: red raspberries, anthocyanins, polyphenols, ellagic acid, diabetes, cardiovascular disease, inflammation, oxidative stress

Introduction

Consuming a diet rich in fruits and vegetables is associated with a reduced risk of several noncommunicable age- and lifestyle-related diseases, including cardiovascular disease (CVD)[5], type 2 diabetes mellitus (T2DM), Alzheimer disease, and cancer (1). The underlying mechanisms continue to be intensely studied; however, risk factor reduction by maintaining or reestablishing "normal" cellular and tissue function is critical to this end. Components of fruits and vegetables that influence the cellular processes that affect pathophysiological (risk) factors may decrease the likelihood of developing chronic diseases. Recent hypotheses have focused on testing health-promoting attributes of fruits and vegetables, such as polyphenols, carotenoids, and other phytochemicals with biological activity.

Red raspberries are becoming increasingly appreciated for their culinary versatility and for their many other applications. This is likely because of increasing consumer interest in health and wellness in parallel with increasing research publications and media communications that describe the unique nutrient and phytochemical composition of red raspberries and their potential role in mitigating disease risk. The key areas of interest in biology include cancer, CVD, diabetes mellitus (DM), and a few publications on body weight changes and neurodegeneration. Other areas of research interest have included the bioavailability of specific components of red raspberries, including the characterization of their metabolites, effects on oxidative stress and inflammation markers, and assessment of their antimicrobial properties—the last of which has potential applications in food safety as well as in human health. Much of the work in these respective areas has been conducted in in vitro cell culture systems, although animal and human studies have been steadily on the rise.

The goal of this review is to focus on the available literature that assesses the health-promoting potential of red raspberries and their select components in modulating the risk of modern-day chronic diseases, specifically CVD, DM, obesity, and Alzheimer disease—all of which share

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[5] Abbreviations used: ARE, antioxidant response element; CVD, cardiovascular disease; DM, diabetes mellitus; eNOS, endothelial NO synthase; IR, insulin resistance; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; T2DM, type 2 diabetes mellitus.
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critical metabolic, oxidative, and inflammatory links. The general approach is to provide a background of each area followed by an accounting and discussion of the research that has tested red raspberries and/or select fractions of their polyphenolic components. Research was identified primarily in Medline with PubMed searches using the following keywords: raspberry, raspberries, red raspberries, polyphenols, anthocyanins, ellagic acid, ellagitannin, cardiovascular disease, heart disease, diabetes, inflammation, oxidative stress, oxidation, body weight, obesity, Alzheimer disease, chronic disease, and bioavailability. Searches were also conducted in the Web of Science and by cross-referencing published articles.

The Red Raspberry: General Overview

The red raspberry (*Rubus idaeus* L.) is a unique berry with a rich history that dates back to the first century when the fruits were gathered from the wild by the people of Troy in the foothills of Mt. Ida (2). Records of domestication were found in the fourth century writings of the Roman agriculturalist Palladius, and seeds have been discovered at Roman forts in Britain. Therefore, the Romans are thought to have spread cultivation throughout Europe (2, 3). In medieval Europe, wild berries were used for medicinal purposes and their juices for paintings and illuminating manuscripts. Today we enjoy these fruits as delicacies of nature cultivated to deliver more than 70 million pounds (~32 million kilograms) per year grown in the leading producing regions of Washington, Oregon, and California (4). Red raspberries account for ~3–4% of total berry production and ~6–7% of utilization (5, 6) and are consumed raw and as a processed (frozen, pureed) ingredient in many dishes, sauces, salads, and drinks.

Red raspberries contribute to the nutritional value of a diet. They are among the highest whole food sources of dietary fiber, providing 6.5 g/100 g of fresh weight, which on a calorie basis is 12.5 g/100 kcal. They also contain vitamin C, magnesium, and a variety of other nutrients, such as potassium, vitamin K, calcium, and iron (**Table 1**) (7). Red raspberries also contain phytochemical components with documented biological activity, many of which were initially investigated based on their in vitro antioxidant properties. Some of these compounds are now recognized for their ability to influence cell signaling pathways that affect receptors, transporters, gene expression, and other cellular events. The package of nutrients and bioactive components that red raspberries deliver suggest their important protective role in human health.

Red Raspberry Phytochemistry

Phytochemicals are secondary plant metabolites that are generally described as nonessential plant nutrients that possess biological activity. Polyphenols constitute one of the largest categories of phytochemicals that provide many functions for plants but are also beneficial when consumed by humans and animals. They are classified into several different categories depending upon their structures and vary from simple phenolic acids (hydroxybenzoic and hydroxycinnamic acids) to complex polyphenols (hydrolysable and condensed tannins) (8, 9). The color and flavor of fruits and vegetables are partly attributed to their phytochemical/polyphenolic components (e.g., lycopene in tomatoes, β-carotene in carrots and sweet potatoes, and anthocyanins in berries) (10). Many of these phytochemicals/polyphenols have been linked to reducing the risk for chronic diseases, including cancer, CVD, DM, and obesity (11–13).

Red raspberries possess a unique polyphenol profile that is characterized primarily by their anthocyanin and ellagitannin content. Anthocyanins are flavonoid compounds and have a basic skeleton of C6-C3-C6. They are responsible for the bright red color of red raspberries. Cyanidin-3-sophoroside, cyanidin-3, 5-diglucoside, cyanidin-3-(2^G-glucosylrutinoside), cyanidin-3-glucoside, cyanidin-3-rutinoside, pelargonidin-3-sophoroside, pelargonidin-3-(2^G-glucosylrutinoside), pelargonidin-3-glucoside, and pelargonidin-3-rutinoside are the major anthocyanins in red raspberries (**Figure 1**A) (14–18). Although all berries contain cyanidin-based anthocyanins, they do not all share similar glycosidic units. The sophoroside unit is a unique cyanidin glycoside in red raspberries. Only strawberries and red raspberries contain pelargonidin-based anthocyanins (19, 20), and the sophoroside attachment is unique to raspberries (21). Red raspberries contain ~92.1 ± 19.7 mg anthocyanins/100 g of fresh fruit in a ratio of 32:1 cyanidin- and pelargonidin-based anthocyanins (22). Anthocyanins in red raspberries contribute ~25% of their antioxidant capacity (14). The total anthocyanin content determined by HPLC varies in different studies because of fruit variety, seasonal differences, developmental stage, and variation in the methods used to quantify the compounds (14, 22–24).

Ellagitannins are the other major group of polyphenols in red raspberries. They are categorized as hydrolysable tannins and are esters of hexahydroxydiphenoyl group that consists of either a glucose or quinic acid core. In addition, galloyl groups may be attached to the glucose core (25, 26). Ellagitannins yield a hexahydroxydiphenoyl molecule upon acid hydrolysis that rearranges to form ellagic acid (Figure 1B), and they are found in only a few plant foods, including strawberries, blackberries, raspberries, cloudberries, pomegranates, muscadine grapes, and some nuts (27). Red raspberries are uniquely known for their sanguiin H-6 (Figure 1C) content. Sanguiin H-6 is the major ellagitannin identified in red raspberries followed by lambertianin C (Figure 1D) (17, 18, 28, 29). Sanguiin H-10 (28, 30), casuarictin/potentilin (28, 31), castalagin/vescalagin, pedunculalagin, and corilagin (28) have been tentatively identified in red raspberries. Because of the complex structure of ellagitannins, their content in red raspberries is typically determined by HPLC after being hydrolyzed to ellagic acid. Like anthocyanins, ellagitannin content varies by variety, season, and quantitative approaches. Mullen et al. (30) indicated that in the Glen Ample cultivar, sanguiin H-6 and lambertianin C accounted for 76 and 31 mg/100 g fresh weight in gallic acid equivalents, respectively. Among 14 cultivars, ellagitannins varied by ~3-fold (14). Seasonal differences can be ~2-fold (23, 29).

TABLE 1 Nutritional content of red raspberries[1]

Component	Raw	Frozen and unsweetened	Frozen and sweetened	Canned in syrup
Water, g/100 g	85.75	85.75	72.75	75.33
Energy, kcal/100 g	52	52	103	91
Protein, g/100 g	1.20	1.2	0.7	0.83
Total lipid (fat), g/100 g	0.65	0.65	0.16	0.12
Ash, g/100 g	0.46	—	0.24	—
Carbohydrate (by difference), g/100 g	11.94	11.94	26.16	23.36
Total dietary fiber, g/100 g	6.5	6.5	4.4	3.3
Total sugar, g/100 g	4.42	4.42	21.76	20.06
Calcium, mg/100 g	25	25	15	11
Iron, mg/100 g	0.69	0.69	0.65	0.42
Magnesium, mg/100 g	22	22	13	12
Phosphorus, mg/100 g	29	29	17	9
Potassium, mg/100 g	151	151	114	94
Sodium, mg/100 g	1	1	1	3
Zinc, mg/100 g	0.42	0.42	0.18	0.16
Copper, mg/100 g	0.090	—	0.105	—
Manganese, mg/100 g	0.670	—	0.65	—
Selenium, µg/100 g	0.2	—	0.3	—
Vitamin C (total ascorbic acid), mg/100 g	26.2	26.2	16.5	8.7
Thiamin, mg/100 g	0.032	0.032	0.019	0.02
Riboflavin, mg/100 g	0.038	0.038	0.045	0.031
Niacin, mg/100 g	0.598	0.598	0.23	0.443
Pantothenic acid, mg/100 g	0.329	—	0.15	—
Vitamin B-6, mg/100 g	0.055	0.055	0.034	0.042
Total folate, µg/100 g	21	21	26	11
Total choline, mg/100 g	12.3	—	10.2	—
Vitamin A, µg RAE/100 g	2	2	3	2
β-Carotene, µg/100 g	12	—	21	—
α-Carotene, µg/100 g	16	—	29	—
Vitamin A, IU/100 g	33	33	60	33
Lutein + zeaxanthin, µg/100 g	136	—	113	—
Vitamin E (α-tocopherol), mg/100 g	0.87	0.87	0.72	0.59
Vitamin K (phylloquinone), µg/100 g	7.8	7.8	6.5	5.2
Anthocyanidins, mg/100 g				
Cyanidin	—	—	22.60	—
Delphinidin	—	—	0.02	—
Pelargonidin	—	—	1.60	—
Flavones, mg/100 g				
Apigenin	—	—	0.01	—
Luteolin	—	—	0.02	—
Flavonols, mg/100 g				
Kaempferol	—	—	0.01	—
Myricetin	—	—	0.03	—
Quercetin	—	—	1.10	—

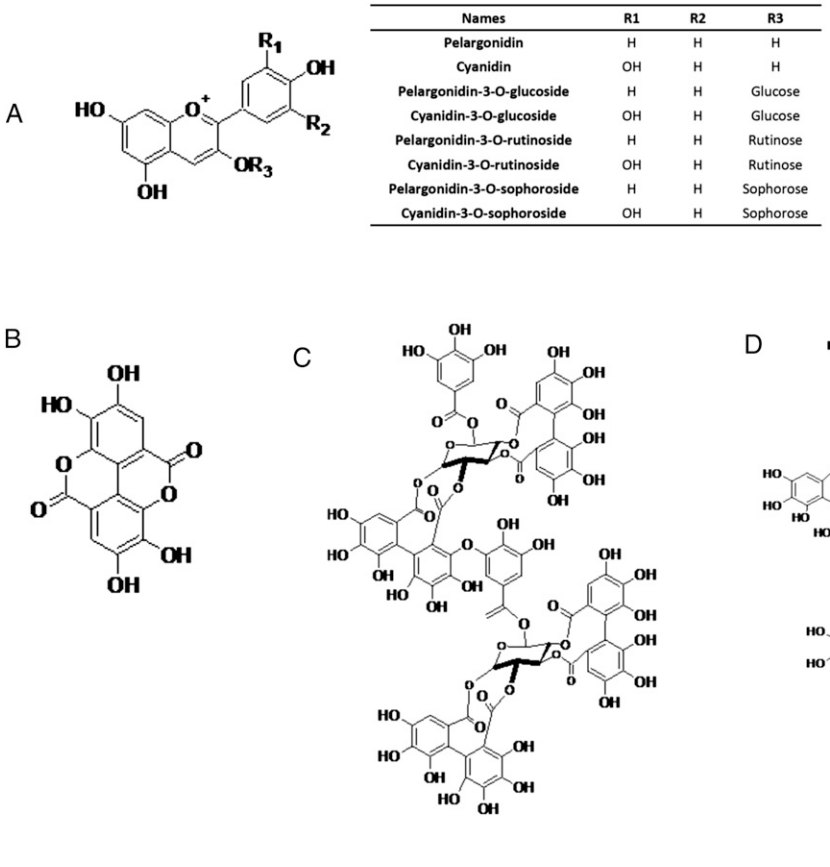
[1] Data from USDA (7). RAE, retinol activity equivalent.

Apart from anthocyanins and ellagitannins, other phenolic compounds such as hydroxycinnamic acids (caffeic, *p*-coumaric, and ferulic acids) (32), hydroxybenzoic acids (ellagic and *p*-hydroxybenzoic acids), flavonols in free and conjugated form (quercetin and kaempferol), and condensed tannins (33) are also present in small quantities in red raspberries. In addition to the genetic and environmental factors that affect the phenolic composition of red raspberries, storage and processing conditions can also affect polyphenol content (34–36).

Bioavailability and Metabolism of Red Raspberry Polyphenols

Bioavailability can be defined as a fraction of ingested compounds that reach the circulatory system and specific tissues/organs to exert biological effects in human health (37). Overall, it is a result of the absorption, distribution, metabolism, and excretion of ingested compounds. The bioaccessibility and bioavailability of polyphenols from red raspberries have been studied in a variety of in vivo and in vitro model systems (38–40), animal models (41), and human intervention trials (42–44).

In general, the polyphenolic components undergo structural modification before being absorbed into the blood. An exception is with the anthocyanins, which can be absorbed intact in their glycated form (45). Structures that escape absorption from the small intestine proceed to the colon, where they are converted to phenolic acids by microorganisms present in the lower bowel, after which they are excreted in feces or absorbed into mesenteric circulation.



Names	R1	R2	R3
Pelargonidin	H	H	H
Cyanidin	OH	H	H
Pelargonidin-3-O-glucoside	H	H	Glucose
Cyanidin-3-O-glucoside	OH	H	Glucose
Pelargonidin-3-O-rutinoside	H	H	Rutinose
Cyanidin-3-O-rutinoside	OH	H	Rutinose
Pelargonidin-3-O-sophoroside	H	H	Sophorose
Cyanidin-3-O-sophoroside	OH	H	Sophorose

FIGURE 1 Structures of major polyphenols in red raspberries: anthocyanidins and anthocyanins (A), ellagic acid (B), sanguiin H6 (C), and lambertianin C (D).

The metabolic products from the colon and the deconjugated phenolics and aglycone structures from the upper digestive tract undergo phase I and II metabolism in the small intestine, liver, and/or kidney, resulting in methylated, glucuronidated, and sulfoconjugated metabolites (46, 47). The resulting metabolites circulate in the blood and are transported to various body tissues and organs. Although some metabolites may never make it into general circulation because of efflux back into the lumen of the intestine after initial enterocyte uptake or because of enterohepatic recirculation, most metabolites are excreted by the kidneys (48).

González-Barrio et al. (49) studied the fate of anthocyanins, ellagic acid, and ellagitannins after healthy human volunteers and individuals with ileostomy consumed 300 g of red raspberries. The outcomes of this study suggested that ~40% of ingested anthocyanins reach the large intestine based on anthocyanins found in the ileal fluid of ileostomy volunteers. These data suggest that ~60% of anthocyanins are absorbed, degraded, or otherwise lost to detection at the level of the small intestine. Similarly, ~23% of the ingested amount of ellagitannins were found in ileal fluid; however, a significant amount of ellagitannins were hydrolyzed to ellagic acid (~241% of intake). In the large intestine, ellagic acid and ellagitannins are principally converted to urolithin metabolites (urolithin A and B). The urolithins undergo phase II metabolism in the wall of the large intestine and in the liver, a process that produces urolithin glucuronides (44). The synthesis of urolithins is mediated by the microbiota of the gut and very specific bacterial strains (*Gordonibacter urolithinfaciens* sp. nov.) (50). Therefore, high interindividual variability in urolithin production has been reported (44, 49). Anthocyanin microbial metabolites are suggested to be from C-ring fission, which releases a variety of phenolic acids that originate from both the A and B rings of the anthocyanin. Vitaglione et al. (51) reported that protocatechuic acid (3,4-dihydroxybenzoic acid) is the principal catabolite of cyanidin-3-*O*-glucoside in humans.

The available data on the bioavailability of raspberry polyphenols echoes the results of others in that the bioavailability of these components seems to be very low. Several factors play a role, including food matrix, dose, interindividual variations, time of intake, complex interactions of polyphenols with other compounds during absorption and digestion, and instrumentation and methodological challenges that result in low values. Isotope studies would advance the field considerably. Nonetheless, a growing body of evidence suggests that polyphenols have biological activity. Continued research in this area will undoubtedly reveal the relation between the fruit composition, intake,

absorption, metabolism, and clearance kinetics of the major polyphenolic components of red raspberries and health/disease risk outcomes. The next several sections review the research published over the past several decades that has 1) examined health/disease risk outcome data associated with metabolic disturbances and 2) concentrated on the biological activity of red raspberry fruit/extract or their predominant phenolic components.

Health Benefits of Red Raspberries and Their Predominant Polyphenolic Components

Cardiovascular disease

CVD causes ~17.5 million deaths per year globally (52). Traditional risk factors are well described (53, 54). Other risk factors such as hemostatic factors, inflammation, insulin resistance, and oxidized LDLs are increasingly recognized for their role and necessity in reducing CVD morbidity and mortality.

Much of the early work in berry research, including red raspberry research, was motivated by the discovery of their antioxidant properties and potential for health benefits (55–57). Although the oxidative stress hypothesis has evolved over the years, oxidative stress and inflammation are paramount in the process of CVD development and arguably many other chronic diseases, such as cancer, diabetes, and Alzheimer disease. The endothelium is among the tissues most vulnerable to oxidative stress and its consequences. Endothelial dysfunction and its role in blood pressure (dys)regulation and atherosclerosis development has earned it a place as an emerging risk factor for CVD and focused research for regulatory claims (58). The role of dyslipemia in CVD development and progression remains a central target for intervention and control in at-risk individuals (59). Understanding how red raspberries affect CVD risk is evolving. The next section reviews the available research on red raspberries. It starts with a general review of oxidative stress and inflammation in CVD development and is followed by a discussion of research that has tested red raspberries in models assessing oxidative stress and inflammation relief, endothelial function, blood pressure regulation, and lipid metabolism.

Oxidative stress and inflammation in CVD. Oxidative stress is characterized by an imbalance between reactive oxygen species (ROS) and antioxidant defenses (60, 61). Oxidative stress increases the risk of oxidative damage to cellular components such as DNA, proteins, and lipids, resulting in impaired cellular function, mutation, and/or cell death. Increasing oxidative stress that leads to oxidative damage has been implicated in the initiation, progression, and complication of cardiovascular diseases (62–65). Within the vessel wall, different oxidants can originate from cellular and extracellular sources and from enzymatic and nonenzymatic pathways (66). Singlet oxygen ($^1O_2$), superoxide (O_2^-), peroxyl (ROO^-) and hydroxyl radicals (OH^-), and peroxynitrite ($ONOO^-$) are examples of ROS that are produced and can cause damaging effects in the human body (67, 68). Sources in the vessel wall include excessive stimulation of nicotinamide adenine dinucleotide phosphate hydrogen oxidase and xanthine oxidase, leakage of mitochondrial electron transport chain products, and uncoupled endothelial nitric oxide synthase (eNOS) (67, 69–73). Another source of oxidation is myeloperoxidase, which is secreted by phagocytic immune cells such as neutrophils, monocytes, and macrophages found in vessel walls and developing atheroma (74). Collectively, the unmanaged ROS can give rise to several modified products, some of which are relevant to the oxidation of LDLs (74, 75), which is involved in foam cell and plaque formation but also relevant in stimulating reduction-oxidation (redox)-sensitive pathways that upregulate the expression of proinflammatory genes. In this way, inflammation and oxidative stress are intimately linked.

NF-κB is a central factor in inflammation. It is a transcription factor that stimulates the encoding of several genes, including those responsible for producing cytokines, chemokines, immunoreceptors, cell adhesion molecules, and acute-phase proteins (76). The activation of NF-κB is redox-sensitive; hence, oxidative stress activates an inflammatory response through NF-κB. Other important mediators of inflammation include pattern recognition receptors such as toll-like receptors and kinases such as MAPK and c-Jun N-terminal kinases. The inflammatory response can be triggered by various stimuli, including cell wall components of bacteria (i.e., LPS), viruses, and changes in the concentrations of ROS, fatty acids, cytokines, growth factors, and carcinogens. In the vessel wall, oxidized LDLs act as important stimuli that cause vascular inflammation and an array of proatherogenic events that lead to atherosclerosis (77).

It has been suggested that anthocyanins can act as prooxidants (by increasing electrophilic compounds such as O_2^- and H_2O_2) that change cellular redox status (78), resulting in various redox-sensitive cell signaling responses, including the stimulation of endogenous antioxidant defense systems. The transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) is redox-sensitive. Under basal conditions, Nrf2 is sequestered mainly in the cytoplasm. When challenged by changes in the redox status, Nrf2 can enhance glutathione synthesis by translocating into the nucleus and promoting the expression of rate-limiting enzymes responsible for glutathione synthesis and inducing the transcription of antioxidant response element (ARE)-dependent antioxidant defense mechanisms. Gut microbial metabolites of anthocyanins, such as phloroglucinol aldehyde from the A ring, may stimulate Nrf2/ARE signaling directly (79). Hence, Nrf2/ARE-dependent mechanisms could play an important role in the effects of raspberries in vivo.

Red raspberries, oxidative stress, and inflammation. Several in vitro cell culture, chemical assay, and enzyme activity studies have been used to assess the possible effects of red raspberry extracts/fractions and purified compounds on indicators of oxidative stress and inflammation. Collectively, the data indicate antioxidative and anti-inflammatory

activity in vitro, as measured by reduced ex vivo LDL oxidation (31, 80, 81), lipid peroxidation (31), DNA damage (82–84), and ROS generation (31, 84) and increases in antioxidant enzyme activity, such as catalase and superoxide dismutase (85). Measures of inflammation have included reduced cytokine production (basal and stimulated) (86–90), NF-κB and MAPK/c-Jun N-terminal kinase activity (85, 90), TLR2 and 4 activation (91), cyclooxygenase activity (90, 92), and PGE_2 production (81).

Increasing our understanding of the potential benefits of red raspberries on oxidative or inflammation endpoints results from performing in vivo animal models. Among the studies identified that tested raspberry extracts (87, 93) or freeze-dried fruit in the diet (94), 2 showed decreased oxidative stress as measured by decreased lipid and protein damage and decreased inflammation in response to raspberry treatment after ~1 mo (87, 93). In a collagen-induced arthritis rat model of inflammation, red raspberry extract (15 mg/kg) significantly reduced the development of clinical signs of arthritis and markedly reduced the degree of bone resorption, soft tissue swelling, and osteophyte formation and thereby prevented articular destruction in animals that received the raspberry extract (95). In a gastritis model, animals treated with ellagitannins, the primary hydrolysable tannin in raspberries, experienced decreased measures of inflammation and increased endogenous antioxidant defenses enzymes, including increased antioxidant enzyme activity catalase and superoxide dismutase (85). In 3 other studies, ellagic acid (hydrolyzed product of ellagitannins) was tested in 1) an immune function model (96), 2) an ex vivo gastritis model (97), and 3) a Crohn disease model (98). In the immune function model, 0.5–2.0 mg ellagic acid/kg showed dose-related suppression of specific immunoglobulin M antibody responses (2.0 mg/kg) and suppressed cytotoxic T cell function (0.5- and 1.0-mg ellagic acid/kg groups), whereas all other immunological parameters, including organ weights, were within normal ranges (96). In the ex vivo gastritis and in vivo Crohn disease models, ellagic acid (0.1–10 g/L and 10–20 mg/kg, respectively) reduced gastric lipid peroxidation (97) and neutrophil infiltration and overproduction of iNOS and COX-2 in intestinal tissue (97, 98). A 100-mg cyanidin-3-glucoside/kg diet was studied in a vitamin E-deficient animal model that resulted in no change in lipid peroxidation and biomarkers of DNA oxidation (i.e., 8-oxo-deoxyguanosine) (82, 99). However, in a recent study that examined crude compared with anthocyanin-rich or -poor fractions of red raspberries in an acute mouse colitis model, the anthocyanin-rich fraction ameliorated symptoms of colitis in the mice, which was consistent with results in LPS-activated RAW264.7 macrophages that showed suppressed inflammatory signaling (e.g., NF-κB, activator protein 1), including downstream gene expression by the anthocyanin-rich fraction (90).

In humans, few studies were identified in the literature that studied the effects of red raspberries on markers of oxidative stress and inflammation, and none exclusively tested red raspberries. The 2 randomized control trials that were identified tested dietary interventions that served a mixture of berries, including raspberries (100, 101). After 2 wk of mixed berries delivered as concentrated juices in a 200-g dessert (with an antioxidant capacity equivalent to 10 servings of fruits and vegetables), measures of oxidative stress did not change in institutionalized elderly men and women (100). In the second study, consumption of mixed berry juice in trained cyclists using an exercise model to induce oxidative stress showed no effect on lipid peroxidation; however, reduced DNA and protein damage were observed in the condition of the berries compared with control (101). Although no conclusions can be drawn relative to raspberries, the trials suggest that berries may be most useful in reestablishing homeostasis or protecting cells/cell components from being damaged during stress situations.

Red raspberries, vascular function, and CVD risk factors. The vascular endothelium is a critical regulator of vascular homeostasis. The endothelium has multiple functions such as regulating thrombosis and fibrinolysis, angiogenesis, and vascular dilator tone (54, 102, 103). Synthesized from L-arginine via eNOS, NO is a central mediator of these functions. Accordingly, a key mechanism underlying endothelial dysfunction is the lack of bioavailable NO (102, 104). Excessive ROS that leads to oxidative degradation of NO is one of the most widely accepted mechanisms involved in altering eNOS/NO signaling pathway, resulting in impaired endothelial function. Diminished NO bioactivity will favor vasoconstriction and potentially result in ischemia; in addition, it can facilitate vascular inflammation, leukocyte adhesion, and foam cell formation—the precursor to atherosclerotic plaque. Therefore, reducing ROS generation and/or providing protection from ROS damage/degradation of NO in endothelial cells has important implications in maintaining endothelial equilibrium and function.

In vitro studies and in vivo animal models have aimed at testing the effects of red raspberry polyphenolic components or red raspberry fruit/extracts on measures that are important for endothelial function. Ellagic acid has been the raspberry constituent of choice among in vivo models. Yu et al. (105) showed that 0–50 μM ellagic acid dose-dependently reduced ROS production in human umbilical vein endothelial cells. Furthermore, ellagic acid inhibited IL-1β-induced nuclear translocation of NF-κB and thereby suppressed the expression of vascular cell adhesion molecule-1 and E-selectin, resulting in decreased monocyte adhesion (**Table 2**). Other in vitro experiments have shown that ellagic acid significantly inhibited oxidized LDL-induced and platelet-derived growth factor-BB-induced proliferation of primary cultures of rat aortic smooth muscle cells via the inactivation of extracellular signal-regulated kinase (Table 2) (106, 107). Methanol extracts of red raspberries have shown anticoagulant and fibrinolytic activity in a series of in vitro assay systems (**Table 3**) (113).

A review of the animal literature revealed 10 studies, 2 of which utilized an ex vivo model of endothelial function (108, 114) and 8 of which evaluated multiple risk factor/marker endpoints after interventions ranging from 5 to16 wk

TABLE 2 Summary of research studies that tested polyphenolic components of red raspberries in CVD models[1]

				Results		
Source (reference)	**Model (study type)**	**Study details**	**Treatment**	**Risk factors/biomarkers**	**Oxidative stress biomarkers**	**Inflammation biomarkers**
Yu (105)	Endothelial cells (in vitro)	Effects of ellagic acid on IL-β-induced formation of intracellular ROS, the translocation of NF-κB, and expression of VCAM-1, ICAM-1, and E-selectin in HUVECs.	0–50 μM EA	Endothelial function: ↔ ICAM-1, ↓VCAM-1, ↓E-selectin	↓ ROS	↓NF-κB translocation, ↓monocyte adhesion
Chang (106)	RASMCs (in vitro)	Effects of ellagic acid on oxidized LDL-induced proliferation of RASMCs. Outcomes: activation of cell signaling kinases, cell cycle changes, and proliferation.	50 μM EA	Endothelial function: ↓RASMC proliferation, ↓PCNA, ↓p-ERK1/2		
Rani (107)	RASMCs; STZ-diabetic rats (in vitro/animal)	Effect of ellagic acid on PDGF-BB-induced proliferation of RASMC primary cultures. Effect of ellagic acid on atherosclerosis development in STZ-induced diabetic rats. Outcomes: cell proliferation, cell cycle changes, ROS, kinase expression and activation; aorta medial thickness and lipid and collagen deposition in the arch of aorta	25 μM EA in vivo; 2% EA (w:w) (animal)	↓Cell proliferation (blocked S-phase entry); ↓cyclin D1; ↓(blocked) PDGF-β-R phosphorylation in vivo (aorta arch); ↓medial thickness; ↓lipid and collagen deposition; ↓cyclin D1 expression in in vivo RASMCs	↓Oxidative stress (ROS), ↓ERK1/2	
Ding (108)	Endothelial cells; mouse aorta rings (in vitro/ animal)	Oxidative stress and HFD-induced endothelial dysfunction and atherosclerosis development was studied in HUVEC and WT C57BL/6 mice and apoE-deficient (−/−) mice. Mice fed HFD (21%) or HFD with EA (HFD + EA) for 14 wk. Oxidative stress induced by HOCl. Outcomes: mouse aortic ring endothelium-dependent relaxation, oxidative stress (HOCl)-induced endothelial dysfunction, eNOS activity, plasma antioxidant capacity, markers of endothelial dysfunction, aortic and HUVEC gene expression.	HFD ± 0.5 g EA/kg diet for 14 wk	Endothelial function: ↑vasodilation, ↑eNOS activity; ↓atherosclerosis in WT HFD + EA vs. WT HFD; ↓plasma endothelial function markers	↓Oxidative stress aortic and HUVEC gene expression, ↑Nrf2, ↑HO-1, ↑plasma AOX	
Chao (109)	Mice (animal)	Diabetic mice were divided into 3 groups (n = 15/group). Normal diet: 2% caffeic acid treatment or 2% EA treatment; control group: nondiabetic mice fed normal diet. Outcomes: variation of biomarkers for hypercoagulability, oxidative stress, and inflammation in cardiac tissue of diabetic mice were measured.	0% or 2% EA (w:w) in diet for 12 wk	↓TG, ↑antithrombin-III, ↓uncontrolled diabetic symptoms	↓Oxidative stress cardiac tissue, ↓MDA, ↓ROS, ↑mRNA AOX enzyme	↓Inflammation in cardiac tissue, ↓IL-1β, ↓IL-6, ↓TNF, ↓MCP-1, ↓mRNA and protein

(Continued)

TABLE 2 (*Continued*)

Source (reference)	Model (study type)	Study details	Treatment	Results		
				Risk factors/biomarkers	Oxidative stress biomarkers	Inflammation biomarkers
Yu (110)	Rabbits (animal)	NZW rabbits (n = 24) assigned randomly to 4 dietary groups. Control/regular rabbit chow, high- fat and cholesterol diet with 0% EA or 1% probucol (w:w) diet. Outcomes: oxidative stress markers, including damage (DNA), atherosclerotic lesion coverage of the intimal surface of the thoracic aorta, expression of caspase-8, caspase-9, and Fas ligand.	0% or 1% EA (w:w) in diet for 8 wk	↓Atherosclerosis, ↓lipids in plasma and aorta	↓TBARS, ↓ROS aortic and DNA damage	↓Caspase-8, ↓caspase-9, ↓Fas ligand
Lin (111)	Doxorubicin-induced mice (animal)	EA against doxorubicin-induced cardiotoxicity (cardiac oxidative, inflammatory, and apoptotic stress were examined). EA supplemented for 8 wk followed by doxorubicin treatment. Outcomes: protection/attenuation of doxorubicin decreases in oxidative defenses, increased oxidative stress and inflammation, and apoptosis in heart tissue	0%, 0.2%, 0.5%, 1% EA (w:w) in diet for 8 wk		↓Oxidative stress heart tissue, ↓MDA, ↓ROS, ↓XO, ↑SOD, ↑GPx, ↑GSH	↓Inflammation in heart tissue, ↓IL-6, ↓MCP-1, ↓dose-related TNF-α, ↓NF-kB, ↓pp38, ↓p-ERK 1/2, ↓p-JNK, ↓caspase3
Panchal (112)	MetS rats (animal)	Diet-induced rat model of MetS. Four groups: HCD or an HCFD with and without EA. EA in food from 8–16 wk only. Outcomes: cardiovascular, hepatic, and metabolic oxidative stress parameters.	HCD or HCFD ± 0.8 g EA/kg for 8–16 wk	↓Impaired ventricular function, ↓glycemia/↓impaired glucose tolerance	↑Nrf2 ,↑CPT1	↓NF-κB in heart and liver

[1] Studies are ordered according to study type (in vitro, n = 2; in vitro/animal, n = 2; animal, n = 4). AOX, antioxidant; CPT1, carnitine palmitoyl transferase 1; CVD, cardiovascular disease; DM, diabetes mellitus; EA, ellagic acid; eNOS, endothelial nitric oxide synthase; ERK 1/2, extracellular signal-regulated kinase 1/2; GPx, glutathione peroxidase; GSH, reduced glutathione; HCD high-cornstarch diet; HCFD, high-carbohydrate, high-fat diet; HFD, high-fat diet; HOCl, hypochlorous acid; H0-1, heme oxygenase 1; HUVEC, human umbilical vein endothelial cell; ICAM-1, intercellular adhesion molecule 1; MetS, metabolic syndrome; MCP-1, monocyte chemoattractant protein 1; MDA, malondialdehyde; Nrf2, nuclear factor erythroid 2-related factor 2; NZW, New Zealand white; PCNA, proliferating cell nuclear antigen; PDGF-β-R, platelet derived growth factor β receptor; p-ERK1/2, phosphorylated ERK1/2; p-JNK, phospho-Jun N terminal kinase; pp38, phosphorylated p38; RASMC, rat aorta smooth muscle cell; ROS, reactive oxygen species; SOD, superoxide dismutase; STZ, streptozotocin; VCAM-1, vascular cell adhesion molecule 1; WT, wild type; XO, xanthine oxidase; ↓, decreased; ↑, increased; ↔, no effect; ±, with or without.

TABLE 3 Summary of research studies that tested red raspberries in models of CVD[1]

Source (reference)	Model (study type)	Study details	Treatment	Results		
				Risk factors/biomarkers	Oxidative stress biomarkers	Inflammation Biomarkers
Torres-Urrutia (113)	Assay (in vitro)	Assessed antithrombotic activity of extracts from 19 fruits, including red raspberry and 26 vegetables. Outcomes: in vitro clotting and fibrin clot lysis times.	1 g raspberry extract/L	Antithrombotic activity: ↑APTT, ↑fibrinolysis, ↔PT, ↔dPT, ↔TT		
Mullen (114)	Aorta rings (in vitro)	Extracts of Glen Ample raspberries, including HPLC fractions of ellagitannins, vitamin C, and anthocyanins. Outcomes: Vasodilation activity using rabbit aortic rings.	Raspberry extract and fractions of extracts	Endothelial function: ↑Vasodilation specific to sanguiin H-6 and lambertianin C		
Suh (115)	Atherogenic hamsters (animal)	Syrian hamsters fed an atherogenic high-fat, high-cholesterol diet with raspberry juice or water for 12 wk. The 3 varieties of red raspberry juice tested were Cardinal, Glen Ample, and Tulameen. Anthocyanin and ellagitannin concentrations were 218–305 μg/mL and 45–72 μg/mL, respectively. Outcomes: cardiac and aortic production of antioxidant enzymes, blood lipids, and BW.	12 wk of 0 or 1 of 3 raspberry varieties	↓TG variety-specific effects on ↓TC, ↓LDL-C, ↑HDL-C, and ↓BW	↓Oxidative stress aorta, ↓ROS, ↑hepatic GPx; variety-specific effects on POX and SOD	
Jia (116)	SHRs and NHRs (animal)	SHRs or age-matched male NHRs fed Xinjiang red raspberry fruit EER. Three groups: water or 100 or 200 mg/(kg × d) EER via gastric gavage daily for 5 wk. Outcomes: SBP, oxidative stress, and vascular relaxation markers.	5 wk of 0, 100, or 200 mg raspberry extract/(kg·d)	↓BP ↓ET, ↑NO; raspberry extract also effective in NHRs on ET and NO	↓Oxidative stress, ↓MDA, ↑SOD; raspberry extract also effective in NHR on MDA and SOD	
Pieszka (117)	Rats (animal)	Male Wistar rats, gavaged daily for 5 wk with seed oils from raspberries, strawberries, and rapeseeds. Outcomes: changes in blood lipid profiles and their effects on selected parameters of oxidative status.	5 wk of 0.8 mL raspberry seed oil/d	↔TG, ↔ TC, ↔LDL-C, ↔HDL-C	↓SOD, ↓GPx	
Freese (118)	Humans: healthy (human intervention)	Randomized control trial. Healthy male and female subjects (n = 77, 19–52 y). Additional 19 healthy controls. Four strictly controlled isocaloric experimental diets containing either 810 or 196 g/10 MJ vegetables, berries, and apple plus either linoleic acid or oleic acid (11–12% of energy, respectively) for 6 wk. Outcomes: markers of platelet function and inflammation.	6 wk of frozen raspberry fruit as part of experimental diet plan	Anti-thrombotic activity: ↔platelet activation, ↔aggregation assay (ADP) ↔PKC, ↔P-selectin		↔ICAM-1, ↔CRP, ↔Thx-b2, ↔aPL-Ab

(Continued)

TABLE 3 (*Continued*)

Source (reference)	Model (study type)	Study details	Treatment	Results		
				Risk factors/biomarkers	Oxidative stress biomarkers	Inflammation Biomarkers
Puupponen-Pimiä (119)	Humans: MetS (human intervention)	Mixture of berries tested in subjects with MetS (n = 20) or controls (n = 12). Berry mixture was 100 g of red raspberries, cloudberries, and strawberries that provided ~71 mg anthocyanins/d and ~789 mg ellagitannins/d. Study conducted for 16 wk: 4-wk run-in, 8 wk of berries, and 4-wk washout. Outcomes: serum lipid profiles, BP, gut microbiota, and ellagitannin metabolites.	16 wk of 0 or 300 g of mixed berries (100 g of raspberries)	↔BP, ↔TC, ↔TG, ↔LDL-C, ↔HDL-C	↔Oxidative stress	

[1] Studies are ordered according to study type (in vitro, n = 2; animal, n = 3; human, n = 2). APTT, activated partial thromboplastin time; aPL-Ab, antiphospholipid antibody; BP, blood pressure; BW, body weight; CRP, C-reactive protein; dPT, diluted prothrombin time; EER, ethyl acetate extract; GPx, glutathione peroxidase; ET, plasma endothelin; HDL-C, HDL cholesterol; ICAM-1, intercellular adhesion molecule-1; LDL-C, LDL cholesterol; MDA, malondialdehyde; MetS, metabolic syndrome; NHR, normotensive Wistar-Kyoto rats; POX, paraoxonase; PT, prothrombin time; ROS, reactive oxygen species; SBP, systolic blood pressure; SHR, spontaneously hypertensive rat; SOD, superoxide dismutase; TC, total cholesterol; Thx-b2, 2,3-dinor-thromboxane B-2; TT, thrombin time; ↓, decreased; ↑, increased; ↔, no effect.

(107, 109–112, 115–117). Increased vasodilation was reported with ellagic acid (Table 2) (108) and raspberry extracts, particularly in response to ellagitannin-rich fractions (Table 3) (114). These results may at least be partly explained by decreased oxidative stress and inflammation in cardiac or vessel tissue, as shown after ellagic acid feeding (107, 108–112) and 12 wk of raspberry juice feeding (115). Ding et al. (108) suggested the effects of ellagic acid may be partly attributed to Nrf2 activation and increased eNOS activity. Collectively, the data suggest improvements in endothelial function, an effect that would also be expected to reduce the risk of hypertension and atherosclerotic development. One study examined blood pressure-lowering effects of 0, 100, or 200 mg red raspberry extracts/(kg·d) in normal and spontaneously hypertensive rats. After 5 wk, the red raspberry extracts demonstrated a dose-dependent antihypertensive effect in spontaneously hypertensive rats, effects that coincided with increased NO activation, decreased vasoconstrictive endothelin-1, dose-specific antioxidative actions, and improved vascular endothelial dysfunction (Table 3) (116).

Atherosclerosis development was tested in a hamster and rabbit model and revealed decreased triglycerides after drinking different varieties of raspberry juice for 12 wk; however, improvements in HDL cholesterol were specific to raspberry variety (var. Cardinal) (Table 3) (115). In New Zealand white rabbits fed a high-fat cholesterol diet supplemented with ellagic acid (1% of the diet) significantly reduced plasma and aorta lipids and significantly decreased atherosclerotic lesion coverage of the thoracic aorta compared with control rabbits (Table 2) (110). These effects coincided with decreased aortic ROS and decreased lipid and DNA oxidative damage and were consistent with a study conducted in streptozotocin-induced diabetic rats that investigated ellagic acid at 2% of the diet (107). Similarly, Panchal et al. (112) showed that ellagic acid attenuated characteristic changes in metabolism, cardiac and hepatic structure, and their respective functions induced by a high-carbohydrate, high-fat diet. The attenuation by ellagic acid may be at least partly explained through the suppression of diet-induced oxidative stress and inflammation. Five weeks of raspberry seed oil (0.8% of diet) supplementation had no effect on blood lipids of rats but increased red blood cell antioxidant enzyme activity (superoxide dismutase and glutathione peroxidase) (Table 3) (117).

In humans, Freese et al. and Puupponen-Pimiä (118, 119) reported, although not exclusively, on how raspberries in 2 randomized control trials affected CVD risk factors. In the former study, frozen raspberries were included in 4 different experimental diets that varied in fruit and vegetable content and type of dietary lipids; the latter included red raspberries as part of a berry mix (300 g of berries, 100 g of which were derived from red raspberries) that was given to recruited subjects with symptoms of metabolic syndrome (119). Both studies reported no differences on blood lipids, blood pressure, and platelet function among interventions (Table 3).

Overall, the animal and in vitro data suggest that raspberries affect emerging (i.e., oxidative stress, inflammation, and endothelial function) and traditional risk factors (i.e., select lipids and lipoproteins and blood pressure) of CVD, and that ellagic acid, the primary breakdown product of ellagitannins, seems to contribute to these effects. The contribution of anthocyanins is not as well described in these models. The human data provided no raspberry-specific insights.

Diabetes mellitus

Recent statistics (120) indicate that ~29.1 million people or 9.3% of the US population have diabetes. Furthermore, ~37% (~86 million) of US adults aged ≥20 y have prediabetes, about half of which are aged ≥65 y. In addition, ~347 million people worldwide currently have diabetes, and projections indicate that it will be the seventh leading cause of death by 2030 (121).

Diabetes is a major risk factor for CVD. Estimates from 2010 indicated that hospitalizations for heart attacks and strokes were 1.8 and 1.5 times higher, respectively, among adults with diagnosed diabetes than adults without diagnosed diabetes. (122). The "common soil" hypothesis suggests that CVD and T2DM share common genetic and environmental antecedents (123). Insulin resistance (IR) is considered one of the most important antecedents that links T2DM and CVD and, more recently, Alzheimer disease (124). IR is most well known for its connection to T2DM. T2DM is preceded by a long period of IR, during which blood glucose is maintained near normal concentrations by compensatory hyperinsulinemia (123). When the cells can no longer compensate for IR by adequately increasing insulin production, impaired glucose tolerance characterized by excessive blood glucose concentrations, and circulating free fatty acid results (123, 125). The concomitant increase in mitochondrial ROS production and intracellular oxidative stress as a result of the excessive influx of energy substrate is thought to be the underlying cause of IR and progression to overt diabetes and CVD (126, 127).

ROS can directly damage cellular macromolecules as well as inactivate or modulate the insulin receptor and insulin receptor substrate function (123, 126, 127). Furthermore, it can also indirectly induce damage to tissues by activating a number of cellular stress-sensitive pathways, some of which are related to inflammation. These pathways have been discussed already and include NF-κB and p38 MAPK (128); each has been identified in the cascade of events that promote the progression and complication of atherosclerosis and now diabetes.

At the cornerstone of preventing and managing diabetes is optimizing lifestyle patterns, including losing weight if overweight or obese, engaging in regular physical activity, and adopting a dietary pattern designed to control hyperglycemia and reduce CVD risk factors such as high blood pressure and dyslipidemia (129, 130). A key dietary recommendation of the American Association of Clinical Endocrinologists is to consume a plant-based diet high in fiber, low in calories and carbohydrates, and high in phytochemicals/antioxidants (130). The nutrient profile of red raspberries and their polyphenolic components (i.e., anthocyanins and ellagitannins/metabolites) make them a candidate for regular inclusion in diets aimed at reducing the risk of diabetes.

Red raspberries and diabetes. Similar to the composition of literature on red raspberries and CVD, most reports that have evaluated polyphenolic components of red raspberries or the fruit/extracts on diabetes or diabetes-related variables are in vitro and in vivo animal studies (109, 112, 131–138) (**Tables 4** and **5**), with limited human studies (139, 140) (**Table 5**).

A purported mechanism for reducing postprandial glucose is to limit glucose absorption by inhibiting α-amylase and α-glucosidase activity. Red raspberry extracts compared to other extracts of berries were most effective in inhibiting α-amylase (131, 132), whereas inhibitory effects on α-glucosidase were intermediate. Raspberry extract fractionation revealed that the unbound anthocyanin-enriched fraction was more effective against α-glucosidase than the original extract, whereas the α-amylase inhibitors were concentrated in the bound fraction. LC-MS-MS identified the inhibitory components as ellagitannins (131). Grusso et al. (132) suggested that proanthocyanidins were important inhibitors of α-amylase activity. Together, the studies suggest that different polyphenolic components of red raspberries may influence different steps in starch digestion and have potential implications for postprandial glycemic control (**Table 5**).

Cell culture models suggest that anthocyanins and anthocyanidins (i.e., aglycones) found in red raspberries can potentially stimulate glucose-mediated insulin secretion from pancreatic β cells (133) to overcome deficits in insulin secretion to manage blood glucose. Other work suggests that anthocyanins enhance insulin sensitivity of fat cells by favorably altering adipocytokine gene expression profiles (i.e., upregulated adiponectin and downregulated inflammatory cytokines) and the phosphoactivation of AMP-activated protein kinase, a fuel gauge to monitor cellular energy status and the therapeutic target for T2DM and obesity management (Table 4) (134, 135).

Studies in diabetic animal models (either genetic or diet-induced) support in vitro findings that showed that 5 wk feeding of cyanidin-3-glucoside (0.2% of diet) reduced fasting glucose and improved insulin sensitivity, as measured by an insulin or glucose tolerance test compared with control groups (136, 137). The effects on metabolic indexes were paralleled by reduced gene expression of inflammatory cytokines in white adipose tissue (136, 137) and upregulated glucose transporter 4 but not adiponectin (136).

In addition to animal studies that examined cyanidin-3-glucoside, a relatively common anthocyanin among berries, other studies using diabetic and metabolic syndrome models have tested the effects of ellagic acid, the hydrolyzed product of ellagitannins, which are more unique to red raspberries. Provided at 2% and 5% of the diet, ellagic acid

TABLE 4 Summary of research studies testing polyphenolic components of red raspberries in models of DM[1]

Source (reference)	Model (study type)	Study details	Treatment	Results		
				Insulin	Glucose	Other
Jayaprakasam (133)	Pancreatic β cells (in vitro)	Individual anthocyanin- or aglycone-treated cells. Outcomes: insulin secretion from pancreatic β cells (INS-1 832/13). Anthocyanins were tested in 4 and 10 mM glucose. Anthocyanin dose was 50 μg/mL except for C3G, which was tested over a 0–250 μg/mL dose range.	50 μg C3G, D3G, C3Gal, Pel3Gal, Cy, Del, Pel, Mal, or Pet/mL	↑Secretion; glucose doses of 4 and 10mM; C3G and D3G > Pel3Gal, Cy, Del, Pel, Mal, and Pet (4 mmol/L); increased Pel 1.4×		
Tsuda (134)	Rat adipocytes (in vitro)	Isolated rat adipocytes, treated with anthocyanins or vehicle (0.1% DMSO). Outcomes: gene expression profiling and protein activation.	100 μM C3G, Cy			Gene expression: ↑adiponectin, ↑leptin (Cy only), ↑PPARγ (Cy only), ↑LPL, ↑UCP2, ↑aP2, and ↑AMPK-P
Tsuda (135)	Adipocytes (in vitro)	Human adipocytes treated with anthocyanins or vehicle (0.1% DMSO) for 24 h. Outcomes: gene expression profiling and GeneChip microarray analysis.	100 μM C3G, Cy			Gene expression: ↑adiponectin, ↓PAI-1, ↓IL-6, ↓UCP2, and ↓acylCoA Ox
Chao (111)	DM mice (animal)	Diabetic mice were divided into 3 groups (n = 15 mice/group): normal diet, 2% caffeic acid treatment, or 2% ellagic acid treatment; control group: nondiabetic mice fed normal diet. Outcomes: variation of biomarkers for hypercoagulability, oxidative stress, and inflammation in cardiac tissues of diabetic mice were measured.	0% or 2% EA (w:w) in diet for 12 wk	↑Insulin	↓Glucose	↓Uncontrolled diabetic symptoms. Cardiac tissue: ↓oxidative stress, ↓inflammation, ↓impaired ventricular function, ↓TG, ↓MDA, ↓ROS, ↓IL-1β, ↓IL-6, ↓TNF, ↓MCP-1, and ↑mRNA AOX enzymes Heart and liver: ↑Nrf2,↑CPT1 ↓NF-κB, ↓ liver fat
Panchal (112)	MetS rats (animal)	Diet-induced rat model of MetS. Four groups: HCD or HCFD with and without ellagic acid. EA in food from 8 to 16 wk only. Outcomes: cardiovascular, hepatic, and metabolic oxidative stress parameters. and	HCD or HCFD ± 0.8 g EA/kg to 16 wk		↓IGT	
Sasaki (136)	T2DM mice (animal)	Type 2 diabetic KK-Ay mice fed control or control +0.2% C3G diet for 5 wk. Outcomes: fasting glucose and insulin, insulin sensitivity, and expression of target proteins in WATs associated with the GLUT4-RBP4 system and related inflammatory adipocytokines.	0.2% C3G (w:w) in diet for 5 wk	↔Insulin, ↑insulin sensitivity	↓Glucose	Gene expression WAT: ↓MCP-1, ↓TNF-α, ↑GLUT4, ↓RBP4, ↔adiponectin
Guo (137)	DIO and db/db mice (animal)	Male C57BL/6J obese mice fed a high-fat diet for 12 wk and genetically diabetic db/db mice. Outcomes: fasting glucose and insulin, insulin sensitivity, and variance in markers of serum and WAT inflammation.	0% or 0.2% C3G (w:w) in diet for 5 wk	↔Insulin, ↑insulin sensitivity	↓Glucose	Gene expression— WAT and serum: ↓MCP-1, ↓TNF-α, ↓IL-6 WAT, ↓c-Jun, ↑FoxO1; liver: ↓liver fat, ↓steatosis

(Continued)

TABLE 4 (*Continued*)

Source (reference)	Model (study type)	Study details	Treatment	Results		
				Insulin	Glucose	Other
Chao (138)	DM mice (animal)	Diabetic mice supplemented with caffeic acid or EA in normal diet: 0, 2.5%, or 5% (w:w) Outcomes: variation of biomarkers in kidney tissue, glucose metabolism, and renal function	0%, 2.5%, or 5% EA (w:w) in diet for 12 wk	↑Insulin	↓Glucose	↓Uncontrolled diabetic symptoms, ↓BW loss, ↓urine out, ↓BUN, ↑creatinine CL, ↓HbA1c, and ↓urinary glycated albumin; renal inflammation: ↓IL-6, ↓IL-1β, ↓TNF, ↓MCP-1

[1] Studies are ordered according to study type (in vitro, $n = 3$; animal, $n = 5$). acylCoA Ox, acyl coenzyme A oxidase; aP2, activating protein 2; AMPK-P (AMP-activated kinase); AOX, antioxidant; BUN, blood urea nitrogen); BW (body weight); CL, clearance; CPT1, carnitine palmitoyltransferase 1; C3G, cyanidin-3-glucoside; Cy, Cyanidin; C3Gal, cyanidin-3-galactoside; Del, delphinidin; D3G, delphinidin-3-glucoside; DM, diabetes mellitus; EA, ellagic acid; FoxO1, forkhead box protein O1; GLUT4, glucose transporter 4; HbA1c, hemoglobin A1c; HCD, high cornstarch diet; HCFD, high-carbohydrate, high-fat diet; IGT, impaired glucose tolerance; INS-1, insulin-producing ß cell line 1; Mal, malvidin; MetS, metabolic syndrome; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; Nrf2, nuclear factor erythroid 2-related factor 2; PAI-1, plasminogen activator inhibitor-1; Pel, pelargonidin; Pel3Gal, pelargonidin-3-galactoside; Pet, petunidin; RBP4, retinol binding protein 4; ROS, reactive oxygen species; TC, total cholesterol; TD2M, type 2 diabetes mellitus; UCP2, uncoupling protein 2; WAT, white adipose tissue; ↓, decreased; ↑, increased; ↔, no effect; ±, with or without.

supplementation for 12 wk increased insulin and reduced fasting glucose, hemoglobin A1c, and glycated urinary albumin, thus improving the uncontrolled diabetic status of the mice (109, 138). Assessments of inflammation and oxidative stress were also improved. Similarly, in rats fed a high-fat, high-carbohydrate diet to induce metabolic syndrome symptoms, 0.8 g ellagic acid/(kg·d) for 16 wk attenuated diet-induced impaired glucose tolerance and diminished diet-induced increases in NF-κB protein concentrations in liver and decreased Nrf2 protein concentrations in the heart and liver (Table 4) (112). Data from the in vitro and in vivo animal studies that tested individual red raspberry compounds and extracts support potential glycemic control actions of red raspberries in humans. Two human studies that assessed the acute glycemic control actions of red raspberries have been published to date (Table 5) (139, 140). Both studies evaluated 2-h insulin and glucose responses to a high-carbohydrate meal with and without red raspberries in relatively healthy individuals. The 12 participants (mean age: 33 ± 13 y) in the study by Clegg et al. (139) consumed 100 g of red raspberries, 50 g of which were cooked in a pancake and another 50 g on top of the pancake. Törrönen et al. (140) served 13 participants (mean age: 50 ± 12 y) 150 g of raspberry puree, with wheat bread supplying 50 g of available starch. Both studies reported no differences between raspberry and control conditions on postprandial glucose or insulin responses (139, 140).

Collectively, the data suggest that red raspberry components have biological activity that could be clinically relevant in preventing or managing diabetes. In vitro studies and in vivo animal data demonstrated antioxidant, anti-inflammatory, and insulin-sensitizing actions in key tissues, specifically adipose tissue. These actions resulted in reduced glycemia and glycated proteins (109, 136–138). Enhancing the pancreatic β cell secretion of insulin is another important mechanism for controlling glucose and slowing disease progression. Both anthocyanins and ellagic acid seem to have insulin secretagogue potential, as demonstrated in cell culture [anthocyanins (133)], in diabetic animals [ellagic acid (109, 138)], and using ligand receptors in in situ docking models (ellagic acid-ATP-sensitive potassium channel) to compare natural compounds to known insulin-secreting drugs [ellagic acid (141)]. The human data did not support the preclinical data, perhaps because of the healthy status of the individuals studied or the acute nature of the design. Overall, data support additional research to better understand the role of red raspberries in reducing diabetes disease risk. Assessments of at-risk individuals as well as in chronic feeding studies that examine insulin sensitivity and associated metabolic outcomes and underlying mechanisms should prove fruitful.

Obesity

More than two-thirds of US adults are overweight or obese, approximately half of whom meet the criteria for obesity. Among young people aged 2–19 y, 31.8% are overweight or obese, ~15% of whom are obese. Obesity has more

TABLE 5 Summary of research studies that tested red raspberries in models of DM[1]

Source (reference)	Model (study type)	Study details	Treatment	Results		
				Insulin	Glucose	Other
McDougall (131)	Enzyme activity (in vitro)	Extracts of SB, RR, BB, BC, or RC. Fractionation of raspberry extract produced an unbound fraction enriched in anthocyanins and a bound fraction enriched in tannin-like polyphenols. Outcomes: inhibition of α-amylase and α-glucosidase.	Raspberry extract			↓α-Amylase activity; RR and SB > BB, BC, and RC ↓α-Glucosidase activity; anthocyanin fraction > tannin fraction
Grusso (132)	Enzyme activity (in vitro)	Extracts from yellow and red raspberries. Outcomes: inhibition of α-amylase.	Yellow and red raspberry extract			↓α-Amylase activity
Clegg (139)	Human: healthy (human intervention)	Randomized control trial. Acute postprandial study of berries with an HC meal. Raspberries or blueberries in (50 g) and atop (50 g) pancakes vs. control pancakes containing similar amounts of fructose and glucose. Outcomes: Glycemic response and satiety index.	Acute 2-h administration of 100 g + HC meal of raspberry fruit		↔Glucose	↔Satiety
Törrönen (140)	Human: healthy (human intervention)	Randomized control trial. Acute postprandial study of berries (individual or mixed) with white wheat bread (WB). Healthy females (n = 13). WB (50 g available starch) with 0 or 150 g whole-berry purée. WB vs WB + various individual berries, including red raspberries. Outcomes: Insulin and glucose response	Acute 2-h administration of 0 and 150 g + WB	↔Insulin	↔Glucose	

[1] Studies are ordered according to study type (in vitro, n = 2; human, n = 2). BB, blueberry; BC, black currant; HC, high carbohydrate; RC, red cabbage; RR, red raspberry; SB, strawberry; WB, white wheat bread; ↓, decreased; ↑, increased; ↔, no effect.

than doubled globally since 1980, and now ~1.9 billion adults are overweight, ~600 million of whom are obese (142). Overweight and obesity are major risk factors for T2DM, CVD, osteoarthritis, nonalcoholic liver disease, and some cancers (143). Obesity is now well recognized to possess and contribute to an excessive inflammatory burden that underlies the pathophysiologies of these diseases. Accordingly, achieving and maintaining a healthy body weight is at the top of lifestyle intervention strategies to reduce chronic disease risk.

Raspberry ketones have attracted mainstream media attention recently for their potential to help people lose weight. The attraction seemed to emanate from research in rodents that reported a reduced weight gain after 5 and 10 wk of raspberry ketone supplementation (2% of diet) with a high-fat diet (**Table 6**) (146). The impetus of the research as indicated by the authors was derived from recognizing structural similarities with capsaicin and synephrine, compounds known to exert antiobese actions and alter lipid metabolism. The study reported raspberry ketone supplementation prevented high-fat, diet-induced elevations in body weight and the weights of liver and visceral adipose tissue (epididymal, retroperitoneal, and mesenteric). In addition, hepatic triacylglycerol content was reduced, whereas norepinephrine-induced lipolysis was significantly increased in rat epididymal fat cells. The authors concluded that raspberry ketones prevent and improve obesity and fatty liver by altering lipid metabolism and specifically by increasing norepinephrine-induced lipolysis in white adipocytes. Follow-up studies in adipocytes (3T3-L1 cells) supported the effects of raspberry ketones on adipocyte lipid metabolism, including increased lipolysis, fatty acid oxidation, and suppressed lipid accumulation (144, 145). Whether additional animal or human trials will support or refute the effects of raspberry ketones remains to be determined. Regardless, the natural abundance of raspberry ketones is low; therefore, achieving concentrations reported in these studies would be challenging.

Examinations of body weight changes in response to red raspberries (fruit) are limited to only 1 study in Syrian

TABLE 6 Summary of research studies that tested polyphenolic components of red raspberries in models of obesity[1]

Source (reference)	Model (study type)	Study details	Treatment	Results		
				Insulin	Glucose	Other
Park (144)	Adipocytes (in vitro)	Elucidated a possible mechanism for the antiobesity action of raspberry ketones in 3T3-L1 adipocytes. Outcomes: expression and the secretion of adiponectin, lipolysis, and fatty acid oxidation.	10 μM raspberry ketones			↑Adiponectin, ↑fatty acid, oxidation, ↓lipid accumulation
Park (145)	Adipocytes (in vitro)	Elucidates a possible mechanism for antiobese actions of raspberry ketones in 3T3-L1 adipocytes treated from days 2 to 8 of differentiation and mature adipocytes for 24 h on day 12 with different doses of raspberry ketone. Outcomes: expression of adipogenic and lipogenic gene expression in 3T3-L1 adipocytes.	1,10, 20, or 50 μM raspberry ketones			↓Dose-dependent adipocyte differentiation, ↓lipid accumulation Dose- and stage-specific effects: ↓PPARγ, ↓C/EBPα, ↓aP2, ↓FASN, ↓ACC1, ↓SCD1 Mature cells: ↑ ATGL, ↑HSL, ↑CPT1B
Morimoto (146)	Mice (animal)	Raspberry ketones on obesity and lipid metabolism. Two interventions: 1) Mice were fed an HFD that included 0.5%, 1%, or 2% raspberry ketone for 10 wk; 2) mice were fed a HFD for 6 wk followed by HFD + 1% raspberry ketones for another 5 wk. Outcomes: BW, liver and adipose tissue weight, hepatic triacylglycerol content, NE-induced lipolysis, HSL, and translocation.	HFD with 0%, 0.5%, 1%, or 2% (w:w) raspberry ketones for 10 wk; 1% raspberry ketone + HFD for 6 wk	↓	↓Fat tissue	↑NE-induced lipolysis, ↑HSL translocation

[1] Studies are ordered according to study type (in vitro, $n = 2$; animal, $n = 1$). ACC1, acetyl-CoA carboxylase-1; aP2, activating protein 2; ATGL, adipose triglyceride lipase; BW, body weight; C/EBPα, enhancer binding protein α; CPT1B, carnitine palmitoyl transferase 1B); FASN, fatty acid synthase; HFD, high-fat diet; HSL, hormone-sensitive lipase; NE, norepinephrine; SCD1, stearoyl-CoA desaturase-1; ↓, decreased; ↑, increased; ↔, no effect.

hamsters (**Table 7**) (115). The hamsters received an atherogenic diet for 12 wk along with water or 1 of 3 juices prepared from Cardinal, Glen Ample, and Tulameen raspberries at a daily dose that corresponded to the consumption of 275 mL by a human that weighs 70 kg. After 12 wk, juice from the Cardinal variety significantly reduced body weight. Various studies have examined and reported a reduction in weight gain with nonraspberry berry interventions and purified anthocyanins in diet-induced obesity models (13, 147, 148); however, the results are not straightforward as they reported either no effect or enhanced weight gain. (13). Compositional differences among the berries, extracts, or compounds being tested, dose, and matrix may all play a role in the results. Red raspberries have a unique composition of polyphenols in a fruit package that is also an excellent source of dietary fiber. Dietary fibers have

TABLE 7 Summary of research study that tested red raspberries in animal models of obesity[1]

Source (reference)	Model (study type)	Study details	Treatment	Results	
				BW	Other
Suh (115)	Hamster (animal)	Syrian hamsters fed an atherogenic high-fat, high-cholesterol diet with raspberry juice or water for 12 wk. Three varieties of red raspberry juice tested: Cardinal, Glen Ample, and Tulameen. Anthocyanins and ellagitannins present at 218–305 μg/mL and 45–72 μg/mL, respectively. Outcomes: cardiac and aortic production of antioxidant enzymes, blood lipids, and BW.	0 or 1 of 3 varieties of raspberry juice for 12 wk	↓Cardinal (only)	↓TG, ↓ variety-specific TC, ↓LDL-C, ↑HDL-C, ↓cardiac aorta ROS, and ↑hepatic GPx; variety-specific effects for POX and SOD

[1] BW, body weight; GPx, glutathione peroxidase; HDL-C, HDL cholesterol; LDL-C, LDC cholesterol; POX, paraoxonase; ROS, reactive oxygen species; SOD, superoxide dismutase; TC, total cholesterol; ↓, decreased; ↑, increased; ↔, no effect.

TABLE 8 Summary of research studies that tested polyphenolic components of red raspberries in models of Alzheimer disease and neuronal health[1]

Source (reference)	Model (study type)	Study details	Treatment	Results	
				Neuronal/behavioral markers	Recovery/other markers
Feng (162)	SH-SY5Y cells (in vitro)	Ellagic acid testing in the cell system at 100 μM for 2, 6, 12, and 24 h on amyloid-β-42 aggregation and neurotoxicity in vitro. Outcomes: fibril and oligomer formation of amyloid-β-42 samples, plaque formation, and neurotoxicity.	100 μM ellagic acid	↑Amyloid β fibril formation; ↑oligomer loss	
Kim (163)	SCI rats (animal)	Rat model of traumatic SCI: vehicle-treated group (n = 20) vs. anthocyanin-treated (C3G) group (n = 20). 14 d treatment post SCI. Outcomes: neurological functions, superoxide expressions, and lesion volumes.	400 mg C3G/kg 14 d after trauma	↓Lesion volume, ↓neuronal loss, ↑motor neuron cells, ↑number of anterior horn motor tasks	↑recovery; ↓oxidative stress
Farbood (164)	TBI rats (animal)	Rat model of TBI. Ellagic acid provided at 100 mg/(kg·d) for 7 d before inducing trauma. Outcomes: passive avoidance memory and hippocampal LTP, BBB permeability, and brain inflammation after TBI.	100 mg ellagic acid/kg 7 d before trauma	↓Memory and hippocampal LTP impairment prevention; ↓IL-1β, ↓IL-6, and ↓BBB permeability	

[1] Studies are ordered according to study type (in vitro, n = 1; animal, n = 2). BBB, blood-brain barrier; C3G, cyanidin-3-glucoside); LTP, long-term potentiation; SCI, spinal cord injury; TBI, traumatic brain injury; ↓, decreased; ↑, increased; ↔, no effect.

been associated with satiety, reduced food intake, and as a strategy for controlling weight (149).

Alzheimer Disease

Alzheimer disease, the most common type of dementia, accounts for an estimated 60–80% of cases (150). It is manifested clinically by progressive memory loss, a gradual decline in cognitive function, and eventually premature death (151). The neuropathological features of Alzheimer disease include the presence of extracellular plaques that contain amyloid-β protein, intracellular neurofibrillary tangles that consist mainly of abnormally phosphorylated τ protein, and dramatic damage and loss of neurons and synapses, especially in the hippocampus and cortex (152, 153). The resulting disease is thought to be the cascade of consequences that result from the accumulated amyloid-β protein—the so-called "amyloid cascade hypothesis." The rate of disease development and progression varies among individuals.

Risk factors for Alzheimer disease are similar to other common chronic diseases. With the exception of rare cases caused by known genetic mutations, Alzheimer disease develops as a result of multiple factors and develops over many years. Advancing age is the greatest risk factor, but Alzheimer disease is not part of normal aging. Other risk factors include family history, apoE genotype, mild cognitive impairment, and cardiometabolic risk factors (150). The metabolic syndrome is a cluster of cardiometabolic risk

TABLE 9 Summary of research study that tested red raspberry in models of Alzheimer's disease and neuronal health[1]

Source (reference)	Model (study type)	Study details	Treatment	Neuronal/behavioral marker results
Fortalezas (165)	Cell (in vitro)	Assessed antioxidant properties of edible strawberry tree fruit vs. raspberry (*Rubus idaeus*) as comparator. Peroxide-induced oxidative stress (1 mM H_2O_2) and pretreatment with dose range of fruit extract. Outcomes: antioxidant capacity of extracts, neuroblastoma viability/survival.	0, 50, 125, and 175 GAE/mL raspberry extract	↑Neuroblastoma survival

[1] GAE, gallic acid equivalent; ↑, increased.

factors that includes abdominal obesity, elevated blood pressure, impaired glucose and insulin metabolism, dyslipidemia, and elevated systemic inflammation—all factors that are associated with CVD and diabetes development. In general, a person who has the metabolic syndrome is twice as likely to develop CVD and 5 times as likely to develop diabetes as someone who does not have metabolic syndrome (154). Metabolic syndrome has also been linked to cognitive impairment, dementia, and the development of Alzheimer disease (155–157). Although the mechanisms underlie the interrelation between cardiometabolic abnormalities and impaired central processing remain to be fully characterized, alterations in peripheral insulin signaling and inflammation seem to be major contributors in Alzheimer pathology (158, 159). Both are involved with accelerated amyloid-β deposition and/or decreased clearance and increased τ phosphorylation and accumulation (158, 159). Therefore, a key to reducing the risk of Alzheimer disease would be to reduce peripheral inflammation and restore insulin sensitivity. Because of age-related increases in oxidative stress and inflammation, approaches with these targeted reductions in mind would likely be favorable in reducing normal age-related cognitive declines as well (160, 161).

Indeed, the studies discussed in previous sections on the relation between red raspberry or its polyphenolic components and improvements in oxidative stress, inflammation, and insulin signaling should be considered promising for reducing Alzheimer disease risk and slowing the aging process. It is important to note that improvements in these biomarkers should coincide with clinically relevant enhancements in cognitive behaviors and reduced pathology (e.g., clearance of amyloid-β protein or decreased deposition). Although no articles were identified in which red raspberries or their major polyphenolic components were consumed in Alzheimer disease models, one assessed the effect of ellagic acid in SH-SY5Y cells and reported that ellagic acid inhibited amyloid-β protein oligomer formation and associated neurotoxicity (**Table 8**) (165). Two other studies assessed the effects of red raspberry extracts (ethanol extract or extracted cyanidin-3-glucoside from red raspberries) for their potential neuroprotective properties in models of neurodegeneration: one study that used a SKN-MC human neuroblastoma cell line (**Table 9**) (165) and a second study that used a rat spinal cord injury model (**Table 8**) (165). Results indicated enhanced cell survivability, reduced neuronal losses, decreased oxidative stress, and improved functional recovery with raspberry extracts compared with controls. Supporting this effect, Farbood et al. (164) reported that feeding rats 100 mg ellagic acid/(kg·d) 7 d before traumatic brain injury significantly prevented memory and hippocampal long-term potentiation impairments and decreased traumatic brain injury-induced elevation in brain IL-1β, IL-6, and blood-brain barrier permeability (Table 8).

Emerging research has highlighted the links between modern-day chronic peripheral (CVD, obesity, and T2DM) and central (Alzheimer) diseases. Although the effect of red raspberries or their components on Alzheimer disease (specifically) is limited, the available data support more research on the role of red raspberries in preserving brain health.

Summary and Conclusions

Red raspberries contribute several valuable essential nutrients and other bioactive components to the diet. Among

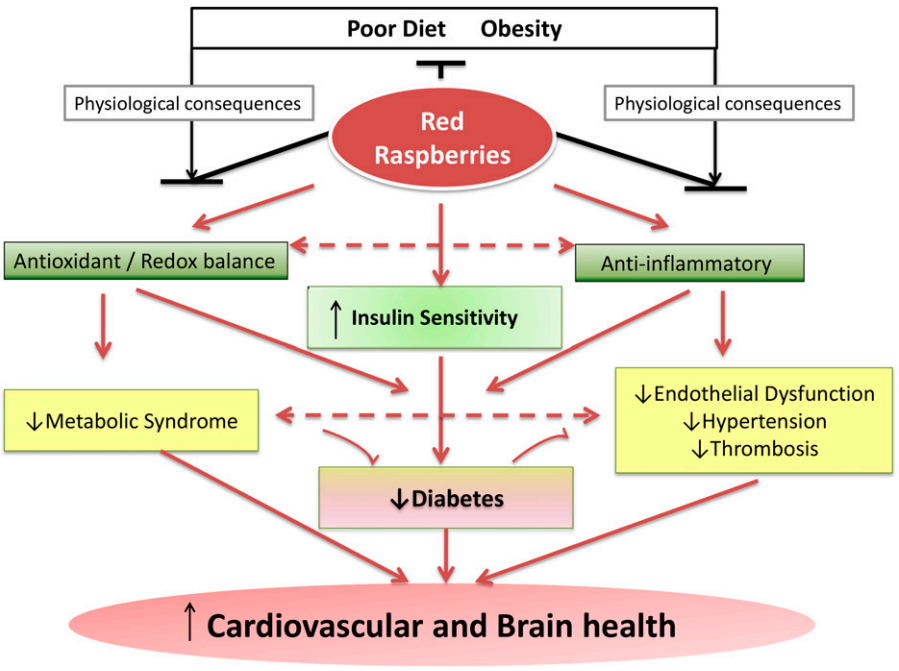


FIGURE 2 The physiological consequences of poor diet and obesity promote metabolic, oxidative, and immune system imbalances, resulting in clinically relevant changes that affect peripheral and central processes that over time lead to chronic diseases, such as cardiovascular disease, diabetes mellitus, and Alzheimer disease. Red raspberries and their predominant polyphenols have been studied in a variety of models for their potential direct and indirect effects on chronic disease mechanisms. The growing literature suggests that red raspberry fruit, including various extracts and individual components, have anti-inflammatory, antioxidative, and metabolic-stabilizing activity. These effects are associated with improvements in blood pressure and lipid profiles, decreased atherosclerotic development, improved vascular function, stabilization of uncontrolled diabetic symptoms (e.g., glycemia), and improved functional recovery from brain injury in preclinical models.

edible plant foods, they provide one of the highest amounts of dietary fiber per 100 kcal and are among the few plant foods that provide a source of ellagitannins and anthocyanins. In vitro studies provide useful data in understanding the potential human health implications of plant bioactivity through their targets and mechanisms of action. However, caution should be exercised in interpreting results from in vitro studies because parent compounds are often applied (instead of a mixture of parent and metabolites as expected in vivo) and often at concentrations that far exceed physiological concentrations. Nonetheless, in vivo animal data have supported many of the in vitro findings, suggesting that red raspberry fruit, including various extracts and individual components, have anti-inflammatory, antioxidative, and metabolic-stabilizing activity. Furthermore, these effects were associated with improvements on relevant endpoints such as reduced blood pressure, improved lipid profiles, decreased atherosclerotic development, improved vascular function, stabilization of uncontrolled diabetic symptoms (e.g., glycemia), and improved functional recovery in brain injury models (**Figure 2**). Indeed, preclinical work dominates the current research; however, the research provides important efficacy and mechanistic data that suggest a key role for red raspberries in reducing the risk for metabolically based chronic diseases, particularly CVD, T2DM, and Alzheimer disease, warranting follow-up research in humans.

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