Cardiovascular Disease Biomarkers in Clinical Use and Their Modulation by Functional Foods

3

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Contents

Abstract

Biomarkers are conventionally defined as "biological molecules that represent health and disease states." Type 2 diabetes, dyslipidemia, and hypertension are strong risk factors for cardiovascular disease (CVD), a leading cause of morbidity and mortality worldwide. Consequently, biomarkers reflecting blood glucose,

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conventional lipid profiles, blood pressure, and inflammation (e.g., C-reactive protein (CRP)), that are routinely used in clinical practice, are effective in predicting CVD. Functional foods, particularly berries, cocoa, and tea have been shown to lower blood glucose and improve insulin sensitivity in some studies, and in most they have beneficial effects on conventional lipids. Soy as a functional food in adults has been associated with lowering of total and LDL cholesterol levels. Emerging evidence supports the role of fruits and vegetables, cocoa, and tea in decreasing CRP, though we did not observe such effects following supplementation of berries and tea in adults with "prediabetes." Consistent observations support the antihypertensive effects of berries, cocoa, and tea in adults with "prediabetes" or advanced CVD. Dietary bioactive compounds, especially polyphenols, have been shown to mediate biological mechanisms that lead to the modulation of clinical biomarkers. Thus, selected functional foods that are commonly consumed in the daily diet hold promise for CVD and can lower levels of biomarkers associated with disease progression.

Keywords

Biomarkers • Berries • Cocoa • Tea • LDL cholesterol • C-reactive protein • Blood pressure

Abbreviations

ALT	Alanine aminotransferase
apoB	Apolipoprotein B
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CHD	Coronary heart disease
CJ	Cranberry juice
CJC	Cranberry juice cocktail
CRP	C-reactive protein
CT	Computed tomography
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DC	Dark chocolate
EGCG	Epigallocatechin gallate
F&V	Fruits and vegetables
FBF	Forearm blood flow
FBG	Fasting blood glucose
FDA	Food and drug administration (US)
FDB	Freeze-dried blueberries
FDS	Freeze-dried strawberries
FFWC	Flavanol-free white chocolate

FMD	Flow-mediated dilatation
FRDC	Flavanol-rich dark chocolate
GT	Green tea
GTE	Green tea extracts
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostatic model assessment of insulin resistance
HTN	Hypertension
IR	Insulin resistance
ISP	Isolated soy protein
LDL-C	Low-density lipoprotein cholesterol
NAFLD	Non-alcoholic fatty liver disease
NCEP	National Cholesterol Education Program
NEFA	Non-esterified fatty acids
NMR	Nuclear magnetic resonance
PJ	Pomegranate juice
QUICKI	Quantitative insulin sensitivity check index
SAA	Serum amyloid A
SBP	Systolic blood pressure
T2D	Type 2 diabetes
TC	Total cholesterol
TG	Triglycerides
TLC	Therapeutic lifestyle change
VCAM-1	Vascular cell adhesion molecule 1
VLDL-C	Very low-density lipoprotein cholesterol

Key Facts Related to Blood Glucose and Lipid/Lipoproteins and Their Modulation by Functional Foods

- Blood glucose values greater than 126 mg/dL (fasting state) and HbA1c greater than 6.5 % are indicative of diabetes.
- Blood lipids, especially LDL cholesterol greater than 120 mg/dL, represent independent risk factor for CVD.
- Berries, especially blueberries and strawberries, lower total and LDL cholesterol and improve insulin sensitivity in adults with CVD risk factors.
- Green tea lowers glucose and LDL cholesterol in adults with the metabolic syndrome, the prediabetic state.
- Whole soy foods lower serum lipids in adults with total cholesterol greater than 200 mg/dL and/or LDL cholesterol greater than 120 mg/dL.
- Polyphenols and other bioactive compounds in functional foods can reduce absorption and metabolism of dietary carbohydrates and lipids.
- Polyphenols and other bioactive compounds in functional foods can increase LDL receptor activity and reduce hepatic cholesterol synthesis.

Key Facts Regarding Inflammatory Biomarkers Modulated by Functional Foods

- Biomarkers of inflammation such as CRP, fibrinogen, and adhesion molecules are indicators of progression of CVD.
- Values of CRP greater than 3 mg/L are indicative of increased CVD risk.
- Fruits and vegetables, cocoa, and tea lower CRP in some reported studies.
- Our research did not find any effects of green tea and berry supplementation on CRP.
- A combination of functional foods may be more effective in lowering inflammation than a single agent.

Key Facts Regarding Modulation of Blood Pressure by Functional Foods

- Hypertension, defined as systolic blood pressure greater than 140 mmHg and/or diastolic blood pressure greater than 90 mmHg, is an independent risk factor for CVD.
- Metabolic syndrome identifies systolic blood pressure greater than 130 mmHg and diastolic blood pressure greater than 85 mmHg as increasing risks of CVD.
- Cocoa, berries, and tea lower blood pressure in many reported studies.
- Our research found blueberries to lower blood pressure in adults with the metabolic syndrome, the prediabetic state.
- Polyphenols and other bioactive compounds in functional foods can improve dilation of the blood vessels.

Definitions

Biomarkers Biological molecules that represent health and disease states; example, blood glucose.

Cardiovascular disease (CVD) A class of diseases that involve the heart or blood vessels; common CVDs include: ischemic heart disease (IHD), stroke, hypertensive heart disease, rheumatic heart disease (RHD), aortic aneurysms, cardiomyopathy, atrial fibrillation, congenital heart disease, endocarditis, and peripheral artery disease (PAD), among others.

C-reactive protein Acute phase protein synthesized by the liver; commonly measured biomarker of inflammation.

Functional foods Foods that provide health benefits beyond basic nutrition; example, green tea.

Hypertension Elevated systolic and diastolic blood pressure; independent risk factor of CVD.

Inflammation Natural immune response; chronic inflammation linked to various diseases, such as CVD and cancer.

LDL cholesterol One of the five major groups of lipoproteins and a common carrier of blood cholesterol typically measured in health and disease states; elevated levels associated with increased risk of CVD.

Metabolic syndrome A "prediabetic state" defined as elevated glucose, elevated blood pressure, elevated triglycerides, reduced HDL cholesterol, and abdominal obesity; any three of these five components confer a diagnosis of the metabolic syndrome.

Polyphenols Major category of plant-based bioactive compounds in foods and beverages shown to confer protection against chronic diseases including cardiovascular disease; exert antioxidant and vasodilator actions among others; example, catechins in green tea

Type 2 diabetes Caused by a progressive insulin secretory defect on the background of insulin resistance; diagnosis involves elevated fasting or 2-h postchallenge blood glucose and/or glycated hemoglobin (HbA1c)

Introduction

Cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, is the leading cause of mortality worldwide, and thus a target for intensive lifestyle and dietary intervention, pharmacological intervention, or both (Go et al. 2013; Roth et al. 2015). Biomarkers, defined as biological molecules that can detect and monitor clinical and subclinical disease burden and response to treatments, have been routinely used in the screening and management of CVD (Jensen et al. 2014). The well-known Framingham Heart Study established the importance of traditional risk factors, such as diabetes, smoking, elevated total cholesterol and reduced high-density lipoprotein (HDL) cholesterol levels, hypertension, and overweight/obesity, as predictors of CVD (D'Agostino et al. 2008). Based on these observations, several algorithms involving CVD biomarkers have been developed to predict an individual's absolute risk of CVD (Jensen et al. 2014; Wenger 2014). The use of biomarkers of glycemia, lipidemia, inflammation (e.g., C-reactive protein (CRP)), and vascular function, such as blood pressure and arterial elasticity, has become an integral part of the clinical care in CVD. These biomarkers have been extensively studied in response to dietary exposures of nutrients and dietary bioactive compounds.

Functional foods and nutraceuticals have gained popularity in the scientific community because of their health benefits that extend beyond basic nutrition, and

several have been shown to exert protective effects against CVD (Crowe and Francis 2013). Berries, cocoa, soy, and tea deserve special attention among the commonly consumed foods and beverages for their cardio-protective effects. The aim of this chapter is to understand the role of these functional foods in modulating CVD biomarkers, based on evidence from clinical studies, including controlled feeding studies reported by our group.

Biomarkers of Blood Glucose and Lipids Are Modulated by Berries, Cocoa, and Tea

Blood glucose and lipid/lipoprotein profiles have been established as biomarkers of type 2 diabetes (T2D) and atherosclerotic CVD in hallmark epidemiological studies and have been extensively used in routine clinical care to identify high-risk populations (Jensen et al. 2014; Wenger 2014). Elevated fasting glucose ($\geq$126 mg/dL) and HbA1c ($\geq$6.5 %) are key diagnostic criteria for diabetes mellitus and are also used to identify the prediabetic state, the metabolic syndrome (fasting plasma glucose 100–125 mg/dL; HbA1c 5.7–6.4 %) (American Diabetes Association 2014). Elevated blood lipids, particularly high LDL ($\geq$120 mg/dL), is an independent risk factor for CVD and a biomarker that is commonly targeted by intervention studies aimed at lowering lipids and subsequent CVD risk (Wenger 2014). Dyslipidemia as characterized by the metabolic syndrome (triglycerides $\geq$150 mg/dL; HDL cholesterol $<$50 mg/dL for women and $<$40 mg/dL for men) is also a risk factor for atherosclerotic CVD, a common vascular complication of diabetes. Based on current understanding of the pathophysiology of insulin resistance, diabetes, and atherosclerotic CVD, multiple pharmacological and non-pharmacological interventions have been developed with the aim of improving blood glucose and lipids, thus lowering risks of vascular complications (Fig. 1).

Berries, cocoa, and tea have demonstrated significant effects in lowering CVD biomarkers, and most of their effects have been attributed to bioactivity of polyphenolic flavonoids, in combination with other compounds, such as phytosterols and fiber in these foods and beverages. In Tables 1 and 2, we present a summary of selected clinical studies that report significant findings on the effects of berries, cocoa, and tea in modulating blood glucose and lipids in participants with one or more CVD risk factors. The baseline ranges of average values of blood glucose and conventional lipids reported in these studies are summarized as follows: glucose (80–155 mg/dL), HbA1c (5.5–7.5 %), total cholesterol (138–239 mg/dL), LDL cholesterol (90–156 mg/dL), HDL cholesterol (38–55 mg/dL), and triglycerides (97–195 mg/dL). Among the 20 studies summarized in Tables 1 and 2, berries, cocoa, or tea supplementation was demonstrated to decrease insulin resistance (improve insulin sensitivity) and/or decrease fasting blood glucose in only eight (Grassi et al. 2008; Stull et al. 2010; Almoosawi et al. 2010; Udani et al. 2011; Sarriá et al. 2014; Nagao et al. 2009; Liu et al. 2014; Mozaffari-Khosravi et al. 2014). On the other hand, berries, cocoa, or tea supplementation was shown to favorably modulate one or more biomarkers of conventional lipid profiles in most of

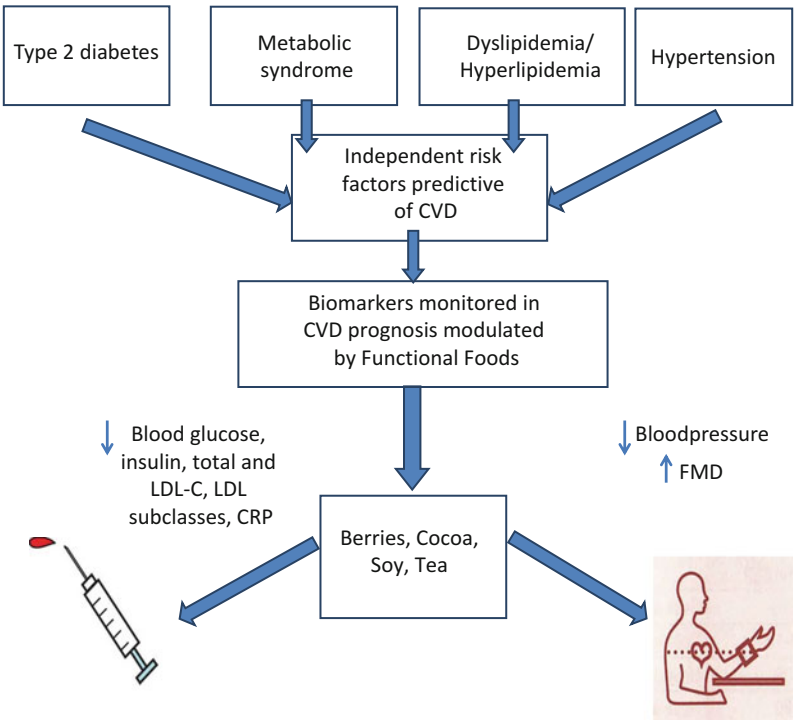

Fig. 1 Clinical biomarkers of CVD and functional foods

the studies reported (Grassi et al. 2008; Udani et al. 2011; Sarriá et al. 2014; Nagao et al. 2009; Liu et al. 2014; Mozaffari-Khosravi et al. 2014; Ruel et al. 2006; Balzer et al. 2008; Mellor et al. 2010; Zunino et al. 2012; Basu et al. 2014, 2010a; Maron et al. 2003; Unno et al. 2005; Nagao et al. 2007; Hsu et al. 2008). We conducted a randomized dose-response feeding trial examining the effects of low (25 g/day) and high (50 g/day) doses of freeze-dried strawberries on glucose and lipid profiles in obese participants with elevated lipids. Our results showed significant decreases in total and LDL cholesterol, as well as nuclear magnetic resonance (NMR)-derived small LDL particle concentrations in the high-dose strawberry group when compared to the controls. No differences were noted in serum glucose, triglycerides, or HDL cholesterol (Basu et al. 2014). In a similar study (Zunino et al. 2012) freeze-dried strawberries were also shown to decrease total cholesterol and increase NMR-derived LDL particle size in obese adults. Another of our studies of people with metabolic syndrome following green tea beverage supplementation (four cups/day) showed trends toward lower LDL cholesterol and higher HDL cholesterol when compared to the unsupplemented controls (Basu et al. 2010). All of these are small studies, but suggest that further research is indicated on the role of berries and green tea in modulating blood glucose and lipids across the spectrum of CVD risks.

Table 1 Modulation of blood glucose and lipids by dietary berries and cocoa in clinical studies of participants with CVD risk factors

Author, year	Study design and duration	Subject characteristics	Intervention	Effects on blood lipids	Effects on blood HbA1c, glucose, insulin, and IR
Ruel et al. (2006)	Placebo phase followed by three successive phases of increasing doses of CJC; 16 weeks	Sedentary men with elevated waist circumference and LDL-C, $n = 30$, mean age = 51 year, BMI = 27.8 kg/m^2	Low-calorie CJC (125 ml, 250 ml, or 500 ml/day)	Increased plasma HDL-C after 250 ml CJC/day; no effects in total-, LDL-, and VLDL-C	Not reported
Grassi et al. (2008)	Randomized crossover; 15 days	Hypertensive men ($n = 11$) and women ($n = 8$) with impaired glucose intolerance, mean age = 45 year; BMI = 26.5 kg/m^2	FRDC or FFWC (100 g/day)	Decreased total and LDL-C after FRDC; no effects on HDL-C and TG	Decreased IR and increased QUICKI; increased insulin sensitivity and beta-cell function after FRDC
Balzer et al. (2008)	Randomized, double-blind, placebo-controlled; 30 days	Adults with T2D, $n = 41$, mean age = 64 year, BMI = 31.6 kg/m^2	Flavanol-rich cocoa (321 mg flavanols) or nutrient-matched control (25 mg flavanols); 3 times daily	Decreased LDL-C only after flavanol-rich cocoa	No significant effects
Stull et al. (2010)	Randomized, double-blind, and placebo-controlled; 6 weeks	Obese, nondiabetic, and insulin-resistant adults, $n = 32$, mean age = 51.5 year, BMI = 37.4 kg/m^2	Blueberry bioactives (22.5 g) or placebo; twice daily	No significant effects	Increased insulin sensitivity after blueberry treatment
Mellor et al. (2010)	Randomized, double-blind, placebo-controlled crossover; 8 weeks	Adults with T2D, $n = 12$, age = 42–71 year, BMI = not reported, body weight at study end = 89 kg	Chocolate with high or low polyphenol content (45 g/day)	Increased HDL-C; decreased total: HDL-C after high-polyphenol chocolate	No significant effects
Almoosawi et al. (2010)	Randomized, single-blind, crossover; 2 weeks	Overweight and obese adults, $n = 14$, age = 21–50 year, BMI = 27.7 kg/m^2	DC (500 mg or 1,000 mg polyphenols); 20 g/day	No significant effects	Decreased FBG with both doses of DC

Udani et al. (2011)	Open label pilot clinical study; 1 month	Overweight adults, $n = 10$, mean age = 28 year, BMI = 27.4 kg/m^2	Acai pulp (100 g) twice daily	Decreased total-C after acai treatment	Decreased FBG and plasma fasting insulin after acai treatment
Zunino et al. (2012)	Randomized, double-blind, placebo-controlled, crossover; 7 weeks	Healthy obese adults, $n = 20$, mean age = 31 year, BMI = 34.0 kg/m^2	Strawberry powder (equivalent to 160 g each serving frozen strawberries) or strawberry-flavored control; twice daily for 3 weeks each	Decreased total cholesterol, NMR-derived small HDL-C particles, increased LDL particle size after strawberry treatment	No significant effects on glucose
Sarria et al. (2014)	Randomized, controlled crossover; 4 weeks	Moderately hypercholesterolemic adults, $n = 20$, mean age = 31 year, BMI = 24.3 kg/m^2	Cocoa product in milk (15 g each serving) twice daily or milk (control)	Increased HDL-C after cocoa treatment; no effect on total- and LDL-C and TG	Decreased FBG after cocoa treatment
Basu et al. (2014)	Randomized, dose-response controlled; 12 weeks	Adults with abdominal obesity and elevated serum lipids, $n = 60$, mean age = 49 year, BMI = 36 kg/m^2	FDS (low dose, 25 g, or high dose, 50 g) or fiber- and calorie-matched control beverages daily	Decreases in total- and LDL-C and NMR-derived small LDL particles in high vs. low dose FDS and vs. high dose controls; no effects on HDL-C and TG	No significant effects on glucose and insulin resistance

The above table is a summary of human intervention studies examining the effects of different forms of dietary berry fruits and juices and cocoa products on levels of blood glucose, conventional lipids, and lipoprotein subclasses in participants with CVD risk factors

Table 2 Modulation of blood glucose and lipids by tea in clinical studies of participants with CVD risk factors

Author, year	Study design and duration	Subject characteristics	Intervention	Effects on blood lipids	Effects on blood HbA1c, glucose, insulin, and IR
Maron et al. (2003)	Randomized, double-blind, placebo-controlled, parallel trial; 12 weeks	Adults with mild to moderate hypercholesterolemia on a low-fat diet, $n = 240$, mean age = 55 year, BMI = 24.2 kg/m^2	Theaflavin-enriched GTE (375 mg polyphenols) or placebo	Decreased total and LDL-C after GTE treatment	Not reported
Unno et al. (2005)	Randomized, triple-crossover postprandial study; 6 h	Adult men with borderline to mild hypertriacylglycerolemia, $n = 9$, mean age = 46 year; BMI = 26.8 kg/m^2	Green tea catechins (10 mg, control), moderate (224 mg), or high (674 mg) dose with a light meal (bread with 20 g butter)	Attenuated postprandial rise of plasma triacylglycerols after green tea treatment; no effects in TC and NEFA	Not reported
Nagao et al. (2007)	Randomized, double-blind, controlled trial; 12 weeks	Adults with abdominal obesity, $n = 240$, mean age = 42 year, BMI = 26.5 kg/m^2	Green tea catechins (583 mg) or control (96 mg) daily	Decreased LDL-C after green tea treatment	No significant effects
Mackenzie et al. (2007)	Randomized, double-blind, placebo-controlled trial; 3 months	Adults with T2D not taking insulin, $n = 49$, mean age = 65 year, BMI = 33.3 kg/m^2	Extracts of green tea and black tea (0, 375 mg or 750 mg polyphenols/day)	Not reported	No significant effects
Hsu et al. (2008)	Randomized, double-blind, placebo-controlled trial; 12 weeks	Obese women, $n = 78$, mean age = 44 year, BMI = 30.9 kg/m^2	GTE (400 mg) three times daily or placebo	Decreased LDL-C and TG, increased HDL-C after GTE treatment	No significant effects

Nagao et al. (2009)	Randomized, double-blind, controlled trial; 12 weeks plus 4-week follow-up	Adults with T2D not taking insulin, $n = 43$, mean age = 64 year, BMI = 24.8 kg/m^2	GT beverage [96 mg (control) or 583 mg catechins/340 mL/]	Decreased total cholesterol and FFA after GT treatment	Decreased HbA1c and increased insulin
Basu et al. (2010b)	Randomized, single-blind, controlled trial; 8 weeks	Adults with the metabolic syndrome, $n = 35$, mean age = 42 year, BMI = 36.3 kg/m^2	Green tea beverage (4cups), green tea extracts (2 capsules), or water (control); EGCG content similar in both green tea groups	Decreasing trend in LDL-C and LDL/HDL and increasing trend in HDL-C after GT treatment	No significant effects
Vieira Senger et al. (2012)	Randomized, controlled trial; 60 days	Adults with the metabolic syndrome, $n = 45$, age $\geq$60 year, BMI = 30.5 kg/m^2	GT (3 cups/day) or no green tea	No significant effects	No significant effects
Liu et al. (2014)	Randomized, double-blind, placebo-controlled trial; 16 weeks	Adults with T2D, $n = 77$, mean age = 54 year, BMI = 26.3 kg/m^2	GTE (500 mg polyphenols/day) three times daily or placebo	Decreased TG, increased HDL-C after GTE treatment	Decreased insulin and HOMA-IR
Mozaffari-Khosravi et al. (2014)	Randomized clinical trial; 4 weeks	Adults with T2D, $n = 94$, mean age = 52 year, BMI = 28.2 kg/m^2	GT or sour tea (150 mL) three times daily	Increased HDL-C after GT and sour tea	Decreased insulin in GT and increased insulin in sour tea group; decreased HOMA-IR in GT vs. sour tea

The above table is a summary of human intervention studies examining the effects of different forms of tea as beverage or extracts on levels of blood glucose, conventional lipids, and fatty acids in participants with CVD risk factors

Many mechanistic studies explain the role of berries, cocoa, and tea bioactive compounds in the management of blood glucose and lipids. The hypoglycemic effects of polyphenols are mainly attributed to their ability to reduce intestinal absorption of dietary carbohydrates, modulation of the enzymes involved in glucose metabolism, improvement of β-cell function and insulin action, stimulation of insulin secretion, and the antioxidative and anti-inflammatory properties of these compounds (McDougall et al. 2005; Munir et al. 2013; Hanhineva et al. 2010). In case of blood lipid/lipoprotein profiles, polyphenols have been shown to decrease lipid absorption from the intestine and formation of micelles, cause inhibition of cholesterol absorption from brush-border membranes, inhibition of cholesterol synthesis, and decreased hepatic secretion of apolipoprotein B (apoB)-100 (Chen et al. 2014; Bladé et al. 2010). Thus, future clinical studies must define the role of berries, cocoa, and tea in modulating blood glucose and lipids in the context of variations in habitual diet, metabolic phenotypes, optimal dosing, and effects of food processing on bioactivities of constituent compounds.

Modulation of Lipids and Lipoproteins by Soy

As shown in many clinical studies and in systematic meta-analyses over the last two decades, soy products, such as soy proteins, soy phytoestrogens, and soy nuts can reduce serum lipids and lipoproteins (Anderson et al. 1995; Zhan and Ho 2005; Anderson and Bush 2011). These beneficial findings have been adopted for the development of preventive strategies against CVD. The US Food and Drug Administration (FDA) approved the health claim that "25 g of soy protein a day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease" (Food and Drug Administration 1999). Table 3 summarizes the effects of soy as a functional food on lipids and lipoprotein profiles in participants with elevated lipids. The baseline range of average values of conventional lipids reported in these studies are summarized as follows: total cholesterol (208–270 mg/dL), LDL cholesterol (136–186 mg/dL), HDL cholesterol (45–62 mg/dL), and triglycerides (112–192 mg/dL). Out of these eight studies, five showed a significant decrease in LDL cholesterol following soy supplementation per se or in combination with a cholesterol-lowering diet (Crouse et al. 1999; Wangen et al. 2001; Tonstad et al. 2002; Blum et al. 2003; Welty et al. 2007). Apolipoprotein B (apoB) was shown to decrease in only one of these studies (Welty et al. 2007), while HDL cholesterol and triglycerides were mostly unaffected. Based on these studies and the meta-analyses, it appears that soy exerts cholesterol-lowering effects largely in participants with elevated total and LDL cholesterol values. Furthermore, clinical responses to soy has also been shown to be modulated by equol production, a product of intestinal bacterial metabolism of soy isoflavone daidzein (Hodis et al. 2011), though not all reported studies comment on the role of equol in modulating the effects of soy on lipid profiles. The mechanisms responsible for the effects of soy on serum lipoproteins continue to being explored, but have been mainly attributed to the role of soy isoflavones in modulating LDL receptor activity

Table 3 Modulation of lipids and lipoproteins by soy in clinical studies of participants with CVD risk factors

Author, year	Study design and duration	Subject characteristics	Intervention	Effects on blood lipids and lipoproteins
Crouse et al. (1999)	Randomized, double-blind, parallel trial; 9 weeks	Moderately hypercholesterolemic adults on a NCEP Step I diet, $n = 156$, mean age = 52 year, BMI = 26 kg/m^2	ISP (25 g with 3 mg, 27 mg, 37 mg, or 62 mg isoflavones/day) or 25 g casein	Decreased total and LDL-C after 62 mg isoflavones from ISP; decreased total and LDL-C after 37 mg isoflavones from ISP daily in high LDL-C group
Wangen et al. (2001)	Randomized, crossover trial; 93 days (three phases)	Normocholesterolemic and mildly hypercholesterolemic postmenopausal women, $n = 18$, mean age = 57 year, BMI = 25.2 kg/m^2	ISP [7 mg (control), 65 mg, or 132 mg isoflavones/day)	Decreased LDL-C after 132 mg isoflavones from ISP; decreased LDL: HDL-C after 65 mg and 132 mg isoflavones from ISP
Tonstad et al. (2002)	Randomized, parallel trial; 16 weeks	Adults with LDL-C $\geq$4 mmol/L, $n = 130$, mean age = 52 year, BMI = 24.9 kg/m^2	ISP (30 g or 50 g/day) and cotyledon fiber or matched casein and cellulose fiber beverage on a lipid-lowering diet	Decreased LDL-C after 30 g and 50 g ISP
Blum et al. (2003)	Randomized, double-blind, placebo-controlled, crossover trial; 6 weeks	Postmenopausal women with hypercholesterolemia, $n = 24$, mean age = 55 year, BMI not reported	Soy protein (25 g/day) or placebo (milk protein)	Decreased total and LDL-C after 25 g soy protein as well as placebo
Welty et al. (2007)	Randomized, controlled, crossover trial; 8 weeks	Healthy normo and hypertensive postmenopausal women, $n = 60$, mean age = 56 year, BMI = 26.7 kg/m^2	Soy nuts (one-half cup/day; 25 g soy protein) or TLC diet	Decreased LDL-C and apoB in hypertensive women after soy nut intake; no effects in normotensive women

(*continued*)

Table 3 (continued)

Author, year	Study design and duration	Subject characteristics	Intervention	Effects on blood lipids and lipoproteins
Hodis et al. (2011)	Randomized, double-blind, placebo-controlled trial; 2.7 years	Postmenopausal women, $n = 350$, mean age = 61 year, BMI = 25.6 kg/m^2	ISP (25 g with 91 mg aglycon isoflavone equivalents) or placebo	Increased HDL-C after 25 g ISP
Liu et al. (2012)	Randomized, double-blind, placebo-controlled trial; 6 months	Postmenopausal women with prediabetes or early untreated T2D, $n = 180$, mean age = 56 year, BMI = 24.5 kg/m^2	15 g milk protein+100 mg isoflavones/day, or 15 g soy protein+100 mg isoflavones/day, or 15 g milk protein (placebo)	No significant effects
Acharjee et al. (2015)	Randomized, controlled, crossover trial; 8 weeks	Healthy postmenopausal women with or without the metabolic syndrome, n = 60, mean age = 54 year, BMI = 28.2 kg/m^2	Soy nuts (one-half cup/25 g soy protein and 101 mg aglycone isoflavones/day) or TLC diet	Decreased TG only after soy nut intake in women with the metabolic syndrome

The above table is a summary of human intervention studies examining the effects of different forms of soy products on blood levels of conventional lipids and lipoproteins in participants with CVD risk factors

and hepatic cholesterol synthesis (Anderson et al. 1995; Zhan and Ho 2005). Thus, whole soy foods rather than isolated soy components, in combination with a healthy diet, in individuals with elevated total and LDL cholesterol may have cholesterol-lowering effects. Further studies are needed to assess these lipid-lowering effects of soy on CVD complications.

Biomarkers of Inflammation Modulated by Flavonoid-Containing Foods and Beverages

A significant amount of information has been gathered in the last few years on the role of functional foods, especially those containing polyphenols, in modulating biomarkers of inflammation. Inflammation has been proposed as the major pathologic mechanism underlying the development and progression of atherosclerotic CVD (Willerson and Ridker 2004). Many surrogate biomarkers of inflammation have been identified and positively correlated with the initiation and progression of endothelial damage leading to atherosclerosis. Some of these key inflammatory

biomarkers are the following: adhesion molecules, C-reactive protein (CRP), cytokines, fibrinogen, and serum amyloid A (SAA). Table 4 summarizes selected intervention studies on the role of polyphenol-containing foods and beverages in modulating biomarkers of inflammation. Among these eight studies, five reported a decrease in CRP, a routinely measured serum biomarker of inflammation in clinical practice (Dong et al. 2011; Kolehmainen et al. 2012; Stote et al. 2012; Moazen et al. 2013; Macready et al. 2014). However, in our own work, we did not observe any significant differences in inflammatory markers, including CRP and adhesion molecules, following blueberry, strawberry, or green tea intervention (Basu et al. 2014, 2010a, b, 2011). It appears that the baseline levels of these biomarkers, study duration, as well as use of single vs. combined functional foods are important factors that underpin differences observed in target inflammatory molecules.

Large-scale prospective cohort studies have shown significant utility of CRP and fibrinogen in predicting cardiovascular events. In these studies, it was demonstrated that following an initial screening with conventional risk factors alone, the additional assessment of CRP or fibrinogen in people at intermediate risk for a cardiovascular event could help prevent one additional event over a period of 10 years for every 400–500 people so screened (Kaptoge et al. 2012). Though CRP levels vary in different populations, a CRP value >3 mg/L has been shown to be independently associated with a 60 % excess risk in incident CHD compared with levels <1 mg/L after adjustment for all Framingham risk variables (Yousuf et al. 2013). Thus, as shown in Table 4, the role of cocoa, fruits and vegetables, soy, and tea in reducing CRP and/or fibrinogen means that their anti-inflammatory functions deserve further evaluation in larger studies of populations with or without CVD complications.

Modulation of Blood Pressure and Vascular Compliance by Berries, Cocoa, and Tea

Hypertension is the strongest risk factor for CVD and is clinically defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg (James et al. 2014). The metabolic syndrome or the "prehypertensive" state identifies cut points of above normal systolic (≥130 mmHg) and diastolic (≥85 mmHg) blood pressure that have also been shown to be associated with increased risk of CVD (Go et al. 2013). Thus, blood pressure, arterial elasticity, and related measures of vascular compliance are common biomarkers of CVD and can be modified by lifestyle modifications including diet and physical activity. The role of polyphenol-containing foods in the management of blood pressure and vascular dysfunction is inherent in the established guidelines for prevention of hypertension, especially those emphasizing the consumption of fruits and vegetables which are naturally high in polyphenols and other cardio-protective nutrients (Kokubo 2014). Table 5 summarizes the role of polyphenol-containing functional foods and beverages in modulating blood pressure and/or markers of endothelial function and arterial compliance. Among these nine studies, five showed decreases in systolic and/or diastolic blood pressure following interventions with berries, tea,

Table 4 Modulation of C-reactive protein and other markers of inflammation by flavonoid-containing functional foods in clinical studies of participants with CVD risk factors

Author, year	Study design and duration	Subject characteristics	Intervention	Effects on CRP	Effects on other biomarkers of inflammation
Basu et al. (2011)	Randomized, controlled trial; 8 weeks	Adults with the metabolic syndrome, $n = 35$, mean age = 42.5 year, BMI = 36.1 kg/m^2	Green tea beverage (4cups), green tea extracts (2 capsules), or water (control); EGCG content similar in both green tea groups	No significant effects	Decrease in SAA
Dong et al. (2011)	Meta-analysis of 14 randomized controlled trials	Postmenopausal women	Soy foods with isoflavones or isoflavone extracts as treatment vs. controls	Decrease in CRP in women with baseline CRP >2.2 mg/L after isoflavone treatment	Not reported
Kolehmainen et al. (2012)	Randomized, controlled trial; 16 weeks	Overweight adults with features of the metabolic syndrome, $n = 27$, mean age = 52 year, BMI = 32.0 kg/m^2	Bilberries (400 g) or control diet daily	Decreasing trends in CRP after bilberry treatment	Decreased inflammation score
Stote et al. (2012)	Randomized crossover trial with increasing doses of cocoa and/or tea flavanols; 5 days each	Adults with obesity and insulin resistance, $n = 19$, mean age = 46 year, BMI = 36.8 kg/m^2	Cocoa (30, 180, 400, 900 mg) or green tea (2.4 g), daily	Decreased CRP in the highest vs. lowest cocoa dose	Decreased fibrinogen after green tea intervention

Moazen et al. (2013)	Randomized, controlled trial; 8 weeks	Adults with T2D, $n = 36$, mean age = 52 year, BMI = 28.0 kg/m^2	FDS beverage (50 g/day) or macronutrient-matched placebo powder	Decreased CRP after strawberry intervention	Not reported
Sakata et al. (2013)	Randomized, double-blind controlled trial; 12 weeks	Patients with NAFLD, $n = 17$, mean age = 51 year, BMI = 29 kg/m^2	Green tea at high (1,080 mg), or low catechin doses (200 mg), or a placebo	Not reported	Decreased serum ALT and improved liver-to-spleen CT attenuation ratio after green tea treatment
Macready et al. (2014)	Randomized, dose-dependent, controlled trial; 6 weeks	Adults with CVD risk factors, $n = 174$, mean age = 51 year, BMI = 27.6 kg/m^2	High-flavonoid F&V; low-flavonoid F&V and habitual F&V	Decreased CRP in the high-flavonoid F&V group	Decreased E-selectin and VCAM
Asgary et al. (2014)	Randomized, controlled trial; 2 weeks	Adults with HTN, $n = 21$, mean age = 53 year, BMI = 27.4 kg/m^2	Pomegranate juice (150 ml) or similar amount of water daily	No significant effects	Decreased VCAM, increased E-selectin

The above table is a summary of human intervention studies examining the effects of different flavonoid-containing functional foods on blood levels of inflammation in participants with CVD risk factors

or pomegranate juice (Brown et al. 2009; Basu et al. 2010a; Hodgson et al. 2013; Mozaffari-Khosravi et al. 2013; Asgary et al. 2014), while others using cocoa or berry supplementation showed no effect on blood pressure but an improvement in flow-mediated dilation (FMD) (Balzer et al. 2008; Dohadwala et al. 2011). The reported studies are mostly in participants on antihypertensive medications. The baseline range of average values of systolic and diastolic blood pressure reported in these studies are 123–136 mmHg and 73–87 mmHg, respectively. We reported blood pressure-lowering effects of freeze-dried blueberries (50 g/day) in obese adults with the metabolic syndrome (Basu et al. 2010b). However, no such effects on blood pressure or markers of endothelial function were noted in other studies reported by our group involving freeze-dried strawberries (Basu et al. 2014) or green tea (Basu et al. 2010) in obese participants with one or more CVD risk factors. Thus, the effects of functional foods may be modulated by their specific makeup of polyphenols and other nutrients and their interaction with vascular function across the disease continuum.

The literature describes several synergistic mechanisms that account for the antihypertensive effect of polyphenols, acting through different molecular targets and improving endothelium-dependent vasodilation. Inflammation, endothelial dysfunction, and oxidation are apparently interrelated mechanisms that play a substantial role in the pathogenesis of hypertension and are mitigated or reversed by functional foods rich in polyphenols (Huang et al. 2013). However, limited clinical data are available and further research is needed to identify the optimal dosing of these foods and beverages for sustained effects on blood pressure in populations at risk of CVD.

Potential Applications to Prognosis, Other Diseases, or Conditions

CVD is often a lifelong disease that begins with the evolution of risk factors that in turn contribute to the development of subclinical atherosclerosis. The onset of CVD itself worsens the prognosis, with great risk of recurrent event, morbidity, and mortality. Biomarkers of blood glucose, lipids, and blood pressure that are commonly used in clinical practice play a critical role in defining the long-term prognosis of diabetes and atherosclerotic CVD. Blood glucose and HbA1c are significant predictors of CVD complications (Cederberg et al. 2010), and thus their modulation by functional foods is a subject of emerging interest in the secondary prevention of these conditions. LDL cholesterol lowering is an important goal: a 2–3 mmol/L reduction is associated with a 40–50 % reduction of CVD "events" (Baigent et al. 2010). In the case of blood pressure control, studies have reported an 18 % risk reduction of stroke mortality with as little as a 5 mmHg reduction in systolic blood pressure (Lackland et al. 2014). Though the magnitude of effects of functional foods is typically less than that of drug interventions, these foods and beverages as part of a long-term daily diet hold promise in the modulation of biomarkers associated with CVD. Thus, future research must identify their effectiveness in high risk

Table 5 Modulation of blood pressure and vascular compliance by selected functional foods and beverages in clinical studies of participants with CVD risk factors

Author, year	Study design and duration	Subject characteristics	Intervention	Effects on systolic and diastolic blood pressure	Effects on markers of endothelial function/ arterial compliance
Balzer et al. (2008)	Randomized, double-blind, placebo-controlled; 30 days	Adults with T2D, $n = 41$, mean age = 64 year, BMI = 31.6 kg/m^2	Flavanol-rich cocoa (321 mg flavanols) or nutrient-matched control (25 mg flavanols); 3 times daily	No significant effects	Increased FMD with cocoa intervention
Brown et al. (2009)	Randomized, double-blind, placebo-controlled trial; 8 weeks	Overweight/obese male adults, $n = 88$, mean age = 51 year, BMI = 31.1 kg/m^2	EGCG capsule (400 mg) twice daily or placebo	Decreased diastolic BP; decreasing trends in systolic BP after EGCG treatment	Not reported
Basu et al. (2010b)	Randomized, single-blind, controlled trial; 8 weeks	Adults with the metabolic syndrome, $n = 35$, mean age = 42 year, BMI = 36.3 kg/m^2	Green tea beverage (4cups), green tea extracts (2 capsules), or water (control); EGCG content similar in both green tea groups	No significant effects	Not reported
Basu et al. (2010a)	Randomized, controlled trial; 8 weeks	Adults with the metabolic syndrome, $n = 48$, mean age = 50 year, BMI = 37.8 kg/m^2	FDB (25 g with 480 mL water) twice daily or control (no blueberries)	Decreased systolic and diastolic BP after blueberry treatment	Not reported
Dohadwala et al. (2011)	Acute uncontrolled pilot study; 4 h and randomized, double-blind, placebo-controlled crossover trial; 4 weeks	Adults with CAD, $n = 59$, mean age = 62 year, BMI = 29.5 kg/m^2	Double-strength CJ (480 mL; 835 mg polyphenols/day) or placebo	No significant effects	Increased FMD after acute CJ dose; decreased carotid-femoral pulse wave velocity after CJ treatment for 4 weeks

(*continued*)

Table 5 (continued)

Author, year	Study design and duration	Subject characteristics	Intervention	Effects on systolic and diastolic blood pressure	Effects on markers of endothelial function/ arterial compliance
Droste et al. (2013)	Randomized, prospective, unblinded trial; 20 weeks	Adults with carotid atherosclerosis, $n = 108$, mean age = 64 year, BMI = 27.6 kg/m^2	Red wine (100 mL for women, 200 mL for men/day) or no alcohol in the setting of a Mediterranean diet and physical activity	No significant effects	Not reported
Hodgson et al. (2013)	Randomized, double-blind, controlled trial; 6 months	Adults with systolic BP between 115 and 150 mmHg and diastolic BP <100 mmHg, $n = 111$, mean age = 57 year, BMI = 25.2 kg/m^2	Powdered black tea solids (3 cups/day with 429 mg polyphenols) or flavonoid-free beverage	Decreased systolic and diastolic BP during nighttime after black tea treatment	Not reported
Mozaffari-Khosravi et al. (2013)	Randomized, clinical trial; 4 weeks	Adults with mild hypertension and T2D, $n = 100$, mean age = 52 year, BMI = 28.2 kg/m^2	GT or sour tea (150 mL) three times daily	Decreased systolic and diastolic BP after GT and sour tea treatment	Not reported
Asgary et al. (2014)	Randomized, controlled trial; 2 weeks	Adults with HTN, $n = 21$, mean age = 53 year, BMI = 27.4 kg/m^2	Pomegranate juice (150 ml) or similar amount of water daily	Decreased systolic and diastolic BP after PJ treatment	Decreased VCAM-1, increased E-selectin after PJ treatment; no effects on FMD

The above table is a summary of human intervention studies examining the effects of different flavonoid-containing functional foods on blood pressure and vascular compliance in participants with CVD risk factors

populations and associations with other novel biomarkers, such as those related to genomics, epigenomics, proteomics, and metabolomics in the prognosis and management of CVD.

Summary Points

- Biomarkers of blood glucose, conventional lipids, CRP, and blood pressure in clinical practice play an important role in prognosis and management of CVD.
- Berries, cocoa, and tea lower blood glucose and lipids (conventional and NMR-derived subclasses) in participants with elevated CVD risk factors.
- Whole soy foods can lower total and LDL cholesterol, most effectively in people with elevated values in conventional lipid profiles.
- Polyphenol-containing fruits and vegetables, berries, and teas lower CRP in a few studies but effect on other inflammatory biomarkers are not well-defined.
- Berries, cocoa, and tea lower systolic and diastolic blood pressure but effect on soluble markers of endothelial function and arterial elasticity are not well-defined.

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