Review Article

Effects of cocoa flavanols on risk factors for cardiovascular disease

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Epidemiologic investigations support the hypothesis that regular consumption of flavonoid-containing foods can reduce the risk of cardiovascular diseases (CVD). While flavonoids are ubiquitous in plants, cocoa can be particularly rich in a sub-class of flavonoids known as flavanols. A number of human dietary intervention trials with flavanol-containing cocoa products have demonstrated improvements in endothelial and platelet function, as well as blood pressure. These studies provide direct evidence for the potential cardiovascular benefits of flavanol-containing foods and help to substantiate the epidemiological data. In this review, results from selective published trials with cocoa and chocolate focused on risk for CVD will be discussed along with a study we recently completed evaluating the effects of the daily consumption of flavanol-containing dark chocolate (CocoaVia™) with and without plant sterol esters on CVD markers in a normotensive population with mild hypercholesterolemia. In this study, the daily consumption of flavanol-containing dark chocolate was associated with a significant mean reduction of 5.8 mmHg in systolic blood pressure. Together the results of these human dietary intervention trials provide scientific evidence of the vascular effects of cocoa flavanols and suggest that the regular consumption of cocoa products containing flavanols may reduce risk of CVD.

Key Words: flavonoids, cocoa, flavanols, cardiovascular, blood pressure

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death in the United States. The costs associated with CVD in the United States alone are estimated at $403.1 billion.[1] World-wide CVD was estimated to account for up to 16.6 million, or one-third of the deaths in 2001 and is predicted to be the leading cause of death in developing countries by 2010.[2] There are multiple factors that are involved with the development of CVD including elevated blood lipids and blood pressure. With the global prevalence of CVD, there is an increasing need for dietary approaches to successfully manage existing, as well as prevent the occurrence of CVD. Foods specially formulated with ingredients that have been proven to prevent and manage known risk factors for CVD offer one option. Over the past decade, there has been increasing interest in a large class of natural plant compounds known as flavonoids, and their potential to improve human health, including cardiovascular health. Multiple epidemiological studies have found an inverse association between the consumption of flavonoid-containing foods and the risk of CVD.[3-5] In addition to these studies which examined flavonoid intake in general, there are also investigations that support that the consumption of specific foods and beverages, including tea, red wine, berries, cocoa and chocolate,[6] are associated with improved cardiovascular outcomes. Given that these beverages and foods can be particularly rich in a sub-class of flavonoids known as flavanols and the structurally related oligomers known as proanthocyanidins, it has been postulated that this specific group of flavonoids may have potent cardioprotective qualities. In line with this, a number of dietary intervention trials with flavanol-containing foods and beverages including teas, grape products, and cocoa products have been published indicating that the consumption of these specific flavanol-containing products can improve the vascular environment. Specific to cocoa, many of these trials have shown that the acute or regular consumption of flavanol-containing cocoa products can improve endothelial function,[7-9] attenuate platelet reactivity,[10-12] improve insulin sensitivity, as well as reduce systolic and diastolic blood pressure.[12] While the mechanisms underlying these effects are still under investigation, these studies provide strong evidence that the consumption of cocoa flavanol-containing foods can improve the vascular environment, and thus, may positively impact cardiovascular health.[13]

The goal of this paper is to provide a brief overview of available data from both epidemiological and human intervention trials with cocoa products, and to discuss the implications of the data to cardiovascular health.

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EPIDEMIOLOGICAL STUDIES

Flavonoids are polyphenolic compounds found in all plants and can be particularly abundant in the human diets. Epidemiological studies support the hypothesis that diets rich in flavonoid-containing plant-based foods have been found to offer significant cardioprotection.[6] Studies examining estimates of flavonoid intake[4] have found a significant inverse correlation between total or specific flavonoid intake and CVD mortality. To date, most of these epidemiological studies have limited their estimates of flavonoid intake to foods in which there exists a published data base on the flavonoid content. With the recent public availability of the US Department of Agriculture's (USDA) flavonoid and proanthocyanidin databases, there are more comprehensive estimates available of flavonoid intake for epidemiological investigations. Earlier this year, Mink *et al.*[14] published the results of a large prospective study in postmenopausal women utilizing the USDA databases to examine the associations between both total flavanoid intake and the intake of the 7 primary subclasses of flavonoids and cardiovascular disease mortality. This latest study using more comprehensive flavonoid estimates did not find an association between total flavonoid intake and cardiovascular mortality; however, specific subclasses of flavonoids (i.e. flavanones and anthocyanidins), and specific foods including apples and pears, strawberries, and chocolate were found to be associated with a reduced risk of CVD mortality.

The identification of the cardioprotective potential of the flavanols in cocoa has been suggested by other studies. In 2006, Buijsse *et al*[5] published a paper evaluating the relationship between the habitual intake of cocoa-containing products and cardiovascular-related mortality in a population of Dutch elderly men. They found that cocoa intake was inversely associated with blood pressure and 15 year cardiovascular and all-cause mortality. In this study, estimates of flavonoid intake were not determined; however, the flavanols in cocoa were suggested to be one mechanism underlying the observed outcomes. In addition, a very recent publication examining death rates among an indigenous group in Panama known to regularly consume very high levels of cocoa beverages containing flavanols found that deaths related to ischemic heart disease, stroke, and diabetes were all significantly lower than among Panamanians who had adopted a more Westernized way of living.[15] While these studies are observational in nature and cannot substantiate cause-and-effect, they do provide interesting population based data that suggests that the regular consumption of cocoa flavanol containing food products may have important cardiovascular benefits.

Intervention trials

A number of human dietary intervention trials with flavanol-containing cocoa products have provided direct evidence in support of their cardiovascular benefits and potential cardioprotective effects. In 1996, the first human study with cocoa found that the acute consumption of cocoa could protect LDL particles from oxidation ex vivo.[16] In addition to reported improvements in antioxidant capacity, more direct evidence in support of potential vascular benefits comes from studies demonstrating an attenuation of platelet reactivity,[10,17] improved vascular function,[9,12,13] improved insulin sensitivity,[12] and reductions in blood pressure[12,13] following the consumption of flavanol-containing cocoa products. The results of the recent meta-analysis, as well as the very recent results of an 18-week randomized, controlled intervention trial with flavanol-containing cocoa[13] provide additional evidence that the consumption of flavanol-containing cocoa can mediate positive changes in blood pressure. Given that blood pressure is a recognized cardiovascular risk factor, the demonstration that the consumption of flavanol containing cocoa can reduce blood pressure within the range of 3-5 mmHg is notable, and if fully substantiated, could have tremendous implications for public health

Recent Intervention study

In the context of the need for products specifically formulated with ingredients that may be used to help manage known cardiovascular disease risk factors, we recently executed a dietary intervention trial with a product formulated to contain plant sterols (PS) and cocoa flavanols. As plant sterols are well-known to reduce cholesterol absorption and thus in turn, lower circulating cholesterol levels,[18] we chose to evaluate if a chocolate bar formulated with PS could effectively lower cholesterol. In addition, we wished to examine if the daily consumption of cocoa flavanols could positively affect blood pressure. For this double-blind, placebo-controlled, cross-over study, 49 mildly hypercholesterolemic, but normotensive men and woman aged between 24-70 years with no other known cardiovascular risk factors were recruited. After a 2-week lead-in period in which subjects were instructed on eating diets consistent with American Heart Association guidelines, subjects were randomized into two treatment groups stratified for total cholesterol, body mass index (BMI), age and sex, and instructed to consume either a chocolate bar with 1.1 g of PS (PS+) or a control bar without added PS (PS-). All bars were matched for macro- and micronutrient content and contained the same quantity of calories (100 kcals/bar), cocoa flavanols (168-193 mg flavanols/bar), theobromine and caffeine; the only difference between bars was the inclusion of PS in the PS+ bar. Subjects were instructed to consume two bars daily, at separate times, either with a meal or within 30 minutes of a meal. At 4 weeks, after all data measures were collected, groups crossed-over to the alternate treatment group for an additional 4 weeks after which final measures were taken at 8 weeks. Seated blood pressure was measured every 2 weeks after resting quietly for 5 minutes. At the end of the 2-week lead in period (identified as the study baseline) and at 4 and 8 weeks, fasting blood samples were drawn on two consecutive days and the results for the lipid outcomes averaged.

Forty-four subjects completed the entire intervention trial. Adherence to the study protocol was good (>90% retention and ~98% of the bars were consumed). Subjects were able to maintain their weight within ±3.5% of

baseline, with a mean weight change of -0.34 ±1.6% (range of -3.4 to + 3.49%). In addition, there were no

Table 1. Blood lipid responses to treatments (Mean ± SD; N = 44)

	Absolute change[1]	Relative Change[2]
Total Cholesterol		
PS+	-0.14 ± 0.45*	-2.0 ± 8.0
PS-	.03 ± 0.51	1.0 ± 9.1
LDL Cholesterol		
PS+	-0.23 ± 0.46	-5.3 ± 11.7
PS-	-0.07 ± 0.45	-1.4 ±11.8

[1] mmol/L; [2] % change from baseline; *different from baseline, $p<0.05$

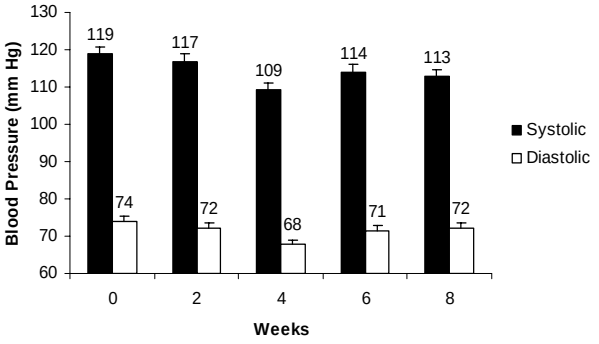

Figure 1. Mean blood pressure over time

significant changes in reported physical activity in either group during the trial ($p> 0.05$).

The regular consumption of plant sterols was able to improve circulating lipids (see Table 1). On average, the regular consumption of the PS+ bar resulted in a 2% reduction in total serum cholesterol level ($p = 0.02$) compared to baseline. This was parallelled by a statistically significant reduction of 5.3% in LDL-C compared to baseline ($p = 0.01$). These treatment effects on total serum cholesterol and LDL-C remained after controlling for change in weight and randomization order. No other treatment effects on lipids were evident based on serum levels of VLDL-C, HDL-C or TG (data not shown). No plant sterol treatment effects were detected in systolic or diastolic blood pressure. However, the consumption of chocolate bars containing cocoa flavanols resulted in significant reductions in systolic and diastolic blood pressures. Within four weeks of initiating the consumption of the chocolate products containing cocoa flavanols, systolic blood pressure decreased by 8.2% ($p< 0.001$), with a 5% reduction relative to baseline still evident at 8 weeks ($p<0.001$). The reduction in diastolic blood pressure was significant at 4 weeks (8.2%, $p < 0.001$) and remained signficant at week 6 (3.4%, $p < 0.05$); however, only a trend towards lower diastolic blood pressure was evident at 8 weeks (2.2%, $p = 0.09$). These results are notable considering that this population was not hypertensive.

The results of this study demonstrate that the regular consumption of products specially formulated with plant sterols and cocoa flavanols can positively impact circulating lipids and blood pressure. Importantly these effects were observed without any adverse effect on weight. Although the effects on blood pressure reported herein are consistent with previously published studies, additional well-designed studies focused on evaluating the effects of these flavanols are clearly warranted before clear recommendations can be made. However, given that cholesterol and blood pressure are two well established modifiable risk factors of CVD, these findings lend support to the concept that the inclusion of these types of specially formulated foods into a balanced diet may help to support cardiovascular health.

CONCLUSIONS

The results of intervention trials, including the study described herein, support that the regular consumption of cocoa products containing flavanols can favorably affect the vascular environment. These data, along with the results from epidemiological investigations, support the notion that in the context of a balanced diet, the inclusion of cocoa products containing flavanols may help to maintain, and perhaps even promote, cardiovascular health. Of course, responsible consumption patterns need to be followed so as to avoid over consumption of calories. In addition, larger studies with well-characterized foods are needed before clear dietary recommendations can be made.

AUTHOR DISCLOSURES

John W Erdman Jr, LeaAnn Carson, Catherine Kwik-Uribe, Ellen M Evans and Robin R Allen, no conflicts of interest, except that Catherine Kwik-Uribe based in Mars Ins.

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