Dietary intake of a specific subclass of flavonoids known as flavanols has attracted increasing interest as a result of recent epidemiological mechanistic and human intervention studies suggesting potential beneficial cardiovascular effects. Among the wide variety of dietary flavanol sources, including apples, cranberries, purple grapes, red wine, and tea, some cocoa and chocolates can be extraordinarily rich in certain types of flavanols.

This article highlights recent studies that have been conducted that provide a growing body of evidence in support of the concept that cocoa flavanols may have a role in improving cardiovascular health. Factors affecting the availability of cocoa flavanols in the diet and limitations that may therefore exist for their application in the public health arena are discussed.

**Dietary Flavanol Intake and Coronary Heart Disease**

Many population-based studies have used dietary surveys to estimate total flavonoid intake or focused on specific dietary sources, with tea most often being the single largest contributor of measured flavonoids. When these studies were designed, it was not widely recognized that cocoa and chocolate could be significant sources of flavanols and, thus, potential contributions from these food sources were not included in dietary questionnaires.

The Zutphen study from Hertog et al. showed a significant inverse relationship between total flavonoid intake and coronary heart disease (CHD) mortality over a five-year follow-up period in elderly men. Hertog et al. also reported beneficial effects of initial high flavonoid intake on CHD mortality over a 25-year period in a total of 16 cohorts drawn from seven countries. However, other studies failed to show a significant relationship between dietary flavonoids and mortality. Studies examining specific foods rich in flavonoids, primarily tea, have suggested a significant relationship between consumption and a reduced risk of myocardial infarction. Unfortunately, with regard to flavanols specifically, there is a paucity of epidemiological data regarding any potential cardiovascular benefits.

**Cocoa Flavanols and Mechanisms of Vascular Action**

Cocoa flavanols have demonstrated the potential to modulate cardiovascular health in at least two important ways: inhibition of platelet activation and improved endothelial function. Rein et al. demonstrated that flavanol-rich cocoa inhibits platelet activation in vivo six hours following its ingestion, with significant reduction in the expression of the surface proteins glycoprotein IIb/IIIa and P-selectin.

In addition to cocoa, a subsequent study found that flavanol-rich chocolate could also inhibit platelet activation in humans. Most recently, a 28-day study found that the consumption of cocoa flavanols reduced platelet aggregation in a group of healthy volunteers, an effect not observed in the group that consumed the matched placebo. Together, these data support the concept that the regular consumption of cocoa flavanols may reduce the activation of platelets and provide a dietary approach to reducing clot formation.

On an acute basis, Pearson et al. directly compared the acute effects of flavanol-rich cocoa and aspirin with respect to inhibition of platelet function. The magnitude of the effect induced by flavanol-rich cocoa was less than that of aspirin, but still statistically significant. Existing data suggest that the primary action of flavanol-rich cocoa with respect to platelet function is to increase the levels of available nitric oxide (NO), decrease the levels of pro-aggregatory leukotrienes, and increase the levels of the anti-aggregatory prostaglandin prostacyclin, with significant reduction in the expression of the surface proteins glycoprotein IIb/IIIa and P-selectin.

More research is needed to determine whether flavanol-rich cocoa can affect other pathways that are important in the prevention of thrombosis.

During the mid 1990s, Hollenberg et al. validated the observation that the Kuna Indians of Panama do not experience an increase in hypertension as they age. This apparent protection was lost in the Kuna when they moved to the urban environment of Panama City. Subsequent dietary research revealed that the Kuna consume large quantities of flavanol-rich cocoa when living in their indigenous environment, but not when they moved to the urban environment of Panama City.
they move to the urban environment.\textsuperscript{2} This observation, coupled with \textit{in vitro} research demonstrating that specific cocoa flavanols could induce aortic ring relaxation via an NO-dependent mechanism,\textsuperscript{3} suggested that the frequent consumption of flavanol-rich cocoa by the Kuna could be one of the protective factors against age-associated hypertension that this population enjoys.

This speculation gained further support following the report of Heiss et al. that consumption of a single flavanol-rich cocoa beverage could transiently improve forearm brachial artery flow-mediated vasodilation.\textsuperscript{5} Importantly, this observation correlated with increased levels of bioavailable NO measured in the blood. Neither an increase in flow-mediated vasodilation nor an increase in bioavailable NO was observed when subjects consumed a low-flavanol cocoa beverage. The increase in bioavailable NO observed \textit{in vivo} is consistent with the hypothesis raised by Karim et al., that the vascular action of cocoa flavanols is, in part, due to their ability to influence NO status.

This hypothesis was confirmed by Fisher et al. in the human study that demonstrated an activation of the NO system following the consumption of a flavanol-rich cocoa beverage.\textsuperscript{4}

Most recently, a study in smokers – a group known to have poor vascular reactivity – demonstrated that the consumption of a cocoa drink rich in flavanols led to significant increases in circulating NO and flow-mediated dilation.\textsuperscript{27} These changes were correlated with increases in flavanol metabolites in plasma. Taken together, these human \textit{in vivo} studies provide support for the concept that cocoa flavanols may help to support cardiovascular health.

\section*{Cocoa Flavanols in the Diet}

Flavanols are a specific class of compounds within the much larger family of polyphenolic compounds known as flavonoids. They occur naturally in a variety of plant-based foods and beverages, including cocoa, chocolates, teas, red wines, fruits, cereals, beans, spices, and nuts.\textsuperscript{28,29} The US Department of Agriculture (USDA) is developing a database that contains information on the flavanol content in many foods and this can be accessed via their website (see Figure 1). The monomeric flavanols (epicatechin and catechin) and the oligomeric flavanols (procyanidins) are present in cocoa and chocolates to a varying extent, depending on the type of cocoa and food processing techniques used to make the finished product.

It is critical to note that the amount and type of flavanols in any food, including cocoa and chocolate products, can vary widely. This point must be considered when evaluating the potential bioactivity of cocoa flavanols regarding cardiovascular health. The amount of flavanols present in finished food products, including cocoa and chocolate, largely depends on the cultivar type, geographical origin, agricultural practices, post-harvest handling, and processing of the flavanol-containing ingredient.\textsuperscript{30} For example, post-harvest handling techniques such as prolonged fermentation and alkalization will greatly reduce or eliminate the flavanol level remaining in a finished cocoa or chocolate product.

\textbf{Table 1} provides an example of how flavanol content can vary in cocoa-based products due to the use of different processing techniques. Other flavanol-containing ingredients used widely in the food industry have similar issues related to content remaining in the finished products. Thus, caution must be used when interpreting flavanol levels likely to be present in specific finished food products based on information derived from raw ingredients or generic food composition tables.

Clinical investigators wishing to ascertain the vascular actions of flavanols in chocolate or cocoa should use only specific products that are well characterized for their flavanol content.

\section*{Notes on Chocolate Specifically}

One of the primary uses of cocoa is the manufacture of chocolate. Chocolate is an energy-dense food and individuals must keep caloric intake and expenditure in mind when including it in their diet, as any food when eaten in excess will cause an increase in weight. Physical activity, diet, and other lifestyle factors must be carefully balanced to avoid detrimental weight gain over time.

In the context of nutrition, one must also consider that the cardiovascular benefits of flavanol-rich foods, including those chocolates that are flavanol-rich, could be offset if they were to simultaneously contribute significant levels of unhealthy fats, such as certain saturated fatty acids that are known to raise blood cholesterol levels. In addition to palmitic acid, chocolate is rich in oleic and stearic acids, and several studies have demonstrated a neutral effect on blood lipids in humans following short-term consumption of cocoa butter and/or chocolate.\textsuperscript{31}

\section*{Potential Cardiovascular Health Applications of Flavanol-rich Cocoa}

The mechanisms of vascular action following the feeding of flavanol-rich cocoa described above suggests potential for use in a variety of applications related to...
cardiovascular health. Recent studies by Grassi et al. and Fisher et al. provide tantalizing hints for what this potential could be. Grassi et al. utilized a cross-over design to study the effects of flavanol-rich dark chocolate and flavanol-poor white chocolate on blood pressure in 20 individuals aged between 25 and 60 years of age with untreated essential hypertension. After 15 days of flavanol-rich dark chocolate consumption, there was a significant reduction in ambulatory blood pressure (24-hour systolic blood pressure: $-11.9 \pm 7.7$ mmHg; 24-hour diastolic blood pressure: $-8.5 \pm 5.0$ mmHg). Improvements in insulin sensitivity and endothelial function were also demonstrated following flavanol-rich dark chocolate consumption for 15 days. These changes were not noted following the consumption of the flavanol-poor white chocolate.

The blood pressure reductions in this study were not observed by Fisher et al. in a shorter duration study of 27 healthy volunteers who drank a flavanol-rich cocoa (821mg per day) in four doses per day. After four days of flavanol-rich cocoa supplementation, blood pressure was measured and then measured again 90 minutes later following consumption of a single dose, with no significant change in blood pressure observed. In addition, low-dose N G-nitro-L-arginine-methyl ester (L-NAME), an NO synthase inhibitor, was infused on days one and five. Before cocoa administration, L-NAME caused a modest increase in systolic blood pressure from $117$ mmHg to $122$ mmHg at 60 minutes ($p=0.03$) and a non-significant increase in diastolic blood pressure, from $68$ mmHg to $71$ mmHg. Interestingly, L-NAME caused a larger increase in systemic blood pressure following four days of flavanol-rich cocoa ingestion. Systolic blood pressure rose from $117$ mmHg to $128$ mmHg (p=0.005) and diastolic blood pressure rose from $66$ mmHg to $71$ mmHg (p=0.004). Presumably, in these healthy volunteers, baroreceptor adjustments were sufficient to minimize the influence of vasodilation induced by flavanol-rich cocoa on blood pressure.

**Conclusion**

Conclusive evidence in the form of large-scale randomized clinical trials is still lacking with respect to the ability of flavanol-rich cocoa to confer cardiovascular health benefits. However, the scientific data that cocoa flavanols may make an important contribution to cardiovascular health continues to grow rapidly. Currently, one important pathway in vascular biology that cocoa flavanols can influence has been identified – NO synthesis. Possibly there are more, e.g. prostaglandin and eicosanoid synthesis.

**Figure 1: Levels of Some Monomeric Flavanols Present in Some Commonly Consumed Flavanol-rich Foods**

<table>
<thead>
<tr>
<th>Product</th>
<th>Total Flavanols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh cocoa beans*</td>
<td>9,776mg/100g</td>
</tr>
<tr>
<td>CocoaPro™ Cocoa Powder*</td>
<td>4,784mg/100g</td>
</tr>
<tr>
<td>Kuna Amerind Cocoa Powder*</td>
<td>3,570mg/100g</td>
</tr>
<tr>
<td>Dove Dark®</td>
<td>185mg/serving (37g)</td>
</tr>
<tr>
<td>M&amp;M® Chocolate</td>
<td>112mg/serving (14g)</td>
</tr>
<tr>
<td>Dark chocolate (highly alkalized)*</td>
<td>3.3mg/serving (37g)</td>
</tr>
</tbody>
</table>

* Unpublished data from Mars, Incorporated.

Human experiments demonstrate that the consumption of flavanol-rich cocoa and chocolate can at least transiently influence platelet function, improve endothelial function, and reduce blood pressure. Unfortunately, as with other flavanol sources such as grapes, tea, and apples, flavanols in cocoa are generally reduced or eliminated during post-harvest handling and production of finished food and beverage products. This indicates that further investment in food technology is required to translate the potential cardiovascular health benefit of flavanols in cocoa into products that can have real public health impact.

This research should be pursued in parallel with further investigation of the potential clinical health benefits for the simple reason that compliance is the ultimate key to public health impact, and cocoa-based products may offer an extraordinary opportunity to successfully improve compliance.
References


29. The United States Department of Agriculture website: http://www.usda.gov/