Recommending Polyphenols for Human Health?  
A Natural Product Research Challenge

Case Study:  
Cocoa Flavanols

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What is Cocoa?

Recommending Polyphenols – Assessment Criteria

1. Characterisation: Is the substance or food constituent adequately defined?
2. Efficacy: Are there sufficient data from adequate epidemiological investigations, clinical trials, and dietary intervention studies demonstrating the efficacy of the substance or food constituent, and is the intake of the substance or food constituent causally related to the observed beneficial effects?
3. Meaningful Benefits: Are the beneficial effects observed meaningful in the context of public health or clinical practice?
4. Effective intake: Are there sufficient data from adequate clinical trials and dietary intervention studies to allow for the determination of the minimum intake amount necessary to achieve a population-based health benefit?
5. Background Dietary Intake: How much of the substance or food constituent are people currently consuming?
6. Mechanisms of Actions: by which the substance or food constituent exert their health benefits known and comprehensively understood?
7. Safety: Are there adequate data to demonstrate the general safety of the substance or food constituent?

WHAT ARE FLAVANOLS?


Use to assess new studies and data

WHAT ARE FLAVANOLS?

(-)Epicatechin  
(+)-Catechin

Monomer(s)  
Procyanidins

Detection  
Time (min)
Complex Composition

The complexity of different polyphenol classes, and even within a class such as cocoa flavanols & procyanidins, highlights:

- the challenge of developing robust analytical techniques to fully characterise natural polyphenol sources,
- the importance of studies using human subjects and the related high costs for such research, and
- the potential for "attractive simplifications" in communication to lead to public perceptions that may not be supported by the science.

Hence the epidemiological data that shapes many perceptions, and simple hypotheses (eg antioxidants and heart health) are often not supported by well designed human intervention studies.

Potential Benefits of Cocoa Flavanols

- Improved Endothelial function – blood flow
- Reduced Platelet Activation (clotting)
- Reduced Inflammation
- Lowering of BP

Some studies used Chocolate, the strongest used products with defined Cocoa Flavanols in both epidemiological and well controlled intervention trials, so how can these results be communicated responsibly?

Yet not all Cocoa contains Flavanols

- Bean selection and Varietal differences
- Processing typically destroys flavanols, and
- We typically consume Chocolate that has a small cocoa content

What must be considered to move from talking about cocoa flavanols as something good, to being an important part of our diet?

- Consistent Terminology: The need for general improvements and consensus with regard to the practical use of the terms ‘flavanols’ and ‘procyanidins’ as well as the standardization of analytical methods and definitions – eg COCOA FLAVANOLS
- Scientific Rigour & Standards: The need for general improvements of the standards and scientific rigor applied in the context of clinical dietary intervention studies and epidemiological investigations, and the interpretation of results
- Plausible Mechanisms of Action: The need for identifying pharmacological targets and the mechanisms of action by which flavanols and procyanidins mediate their biological effects in vivo (Actually well progressed for endothelial function and BP)
- Population Intake data: The need for more comprehensive information on the population-based intake of dietary flavanols and procyanidins, as well as on safety in the specific contexts of public health and medical practice

Conclusions: Cocoa Flavanols & Human Health

• Epidemiological data is highly supportive
• Cocoa Flavanols have been well characterised
• Analytical Methods and Standards are published & in use

• Multiple, well controlled human studies have demonstrated consistent results:
  - absorption & bioavailability
  - metabolism
  - beneficial effects on Endothelium Function & BP
• Plausible Mechanisms of Action have been postulated, tested and demonstrated in a wide range of subject groups
  (NO mediated endothelial dilatation)

• Acute intake levels have been established, chronic beneficial intake levels await confirmation

Communication of Benefits remains a Challenge ..........

Further References & Recommendations
Recommending flavanols and procyanidins for cardiovascular health: Current knowledge and future needs
Hagen Schroeter, Christian Heiss, Jeremy P.E. Spencer, Carl L. Keen, Joanne R. Lupton, Carl L. Keen, Harold H. Schmitz
Mol Aspects Med. 2010 Dec;31(6):546-57

Assessment Criteria:

1. Is the substance or food constituent adequately defined?
2. Are there sufficient data from adequate epidemiological investigations, clinical trials, and dietary intervention studies demonstrating the efficacy of the substance or food constituent, and is the intake of the substance or food constituent causally related to the observed beneficial effects?
3. Are the beneficial effects observed meaningful in the context of public health or clinical practice?
4. Are there sufficient data from adequate clinical trials and dietary intervention studies to allow for the determination of the minimum intake amount necessary to achieve a population-based health benefit?
5. How much of the substance or food constituent are people currently consuming?
6. Are the mechanisms of actions by which the substance or food constituent exert their health benefits known and comprehensively understood?
7. Are there adequate data to demonstrate the general safety of the substance or food constituent?

Nevertheless, it is important to acknowledge that despite the progress made, serious gaps and shortfalls with regard to available data and overall understanding continue to exist. In order to provide final and conclusive data on the health benefits of dietary flavanols and procyanidins in the context of public health or clinical practice it will be essential to identify and to address those gaps and shortfalls. The four most crucial issues include:

- The need for general improvements and consensus with regard to the practical use of the terms ‘flavanols’ and ‘procyanidins’ as well as the standardization of analytical methods and definitions
- The need for general improvements of the standards and scientific rigor applied in the context of clinical dietary intervention studies and epidemiological investigations
- The need for identifying pharmacological targets and the mechanisms of action by which flavanols and procyanidins mediate their biological effects in vivo
- The need for more comprehensive information on the population-based intake of dietary flavanols and procyanidins [considering geographic, ethnic, and socioeconomic, and health status differences], as well as on safety in the specific contexts of public health and medical practice

Applied: objective mediator criteria

the test compound should be absorbed by humans, and it should be transported to the appropriate site or tissue, as indicated by its hypothesized effects;

quantitative assessments should indicate that the amount of the test compound present is sufficient to mediate the hypothesized effect, and that the pharmacokinetics of the test compound (absorbed under physiologically relevant conditions) is not in conflict with effect-specific pharmacodynamics;

if the test compound is a food constituent, the effect mediated by the pure, and chemically identified food constituent should closely mimic physiological effects;

the withholding, (or reduction in intake), of foods containing the test compound, or the withholding of the test compound itself, should be consistent with a reversal or an attenuation of the observed effect; and

the inhibition of endogenous mediator pathways, hypothesized to be causally linked to the effect exerted by the test compound, should result in an attenuation of such effects.

Recent Research results – Cocoa Flavanol benefits in diabetic subjects

- Scientists have found that consuming cocoa flavanols – naturally occurring compounds in cocoa – may offer a benefit to those affected by type 2 diabetes.

- Consuming a cocoa flavanol-rich beverage daily may have the potential to positively impact the blood vessel dysfunction associated with diabetes, suggests a first-of-its-kind study recently published in the Journal of the American College of Cardiology by an international group of scientists.

- Study participants who regularly consumed a cocoa flavanol-rich beverage made using the Mars, Incorporated Cocoapro® process experienced a 30 percent improvement in measured vessel function at the completion of a 30-day trial

(Baltzer, J. J Am Coll Cardiol 2008;51:2141–9)
Sustained Benefits in Vascular Function Through Flavanol-Containing Cocoa in Medicated Diabetic Patients a Double-Masked, Randomized, Controlled Trial

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J Am Coll Cardiol 2008;51:2141–9

Objectives Our goal was to test feasibility and efficacy of a dietary intervention based on daily intake of flavanol-containing cocoa for improving vascular function of medicated diabetic patients.

Background Even in fully medicated diabetic patients, overall prognosis is unfavorable due to deteriorated cardiovascular function. Based on epidemiological data, diets rich in flavanols are associated with a reduced cardiovascular risk.

Methods In a feasibility study with 10 diabetic patients, we assessed vascular function as flow-mediated dilation (FMD) of the brachial artery, plasma levels of flavanol metabolites, and tolerability after an acute, single-dose ingestion of cocoa, containing increasing concentrations of flavanols (75, 371, and 963 mg). In a subsequent efficacy study, changes in vascular function in 41 medicated diabetic patients were assessed after a 30-day, thrice-daily dietary intervention with either flavanol-rich cocoa (321 mg flavanols per dose) or a nutrient-matched control (25 mg flavanols per dose). Both studies were undertaken in a randomized, double-masked fashion. Primary and secondary outcome measures included changes in FMD and plasma flavanol metabolites, respectively.

Results A single ingestion of flavanol-containing cocoa was dose-dependently associated with significant acute increases in circulating flavanols and FMD (at 2 h: from 3.7  0.2% to 5.5  0.4%, p  0.001). A 30-day, thrice-daily consumption of flavanol-containing cocoa increased baseline FMD by 30% (p  0.0001), while acute increases of FMD upon ingestion of flavanol-containing cocoa continued to be manifest throughout the study. Treatment was well tolerated without evidence of tachyphylaxis. Endothelium-independent responses, blood pressure, heart rate, and glycemic control were unaffected.

Conclusions Diets rich in flavanols reverse vascular dysfunction in diabetes, highlighting therapeutic potentials in cardiovascular disease. (J Am Coll Cardiol 2008;51:2141–9)