Assessing the respective contributions of dietary flavanol monomers and procyanidins in mediating cardiovascular effects in humans: randomized, controlled, double-masked intervention trial

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BACKGROUND

- **Cocoa flavanol intake** in humans has been linked to improvements in **vascular function and health**
- **Cocoa flavanols comprise** several compounds, including **catechin and epicatechin, as well as procyanidins**
- **Epicatechin** belongs to flavanol monomers with a degree of polymerization **of 1 (DP1),** while procyanidins belong to oligomeric **flavanols with a DP of 2-10 (DP2-10)**

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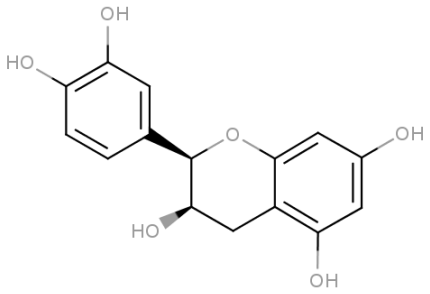
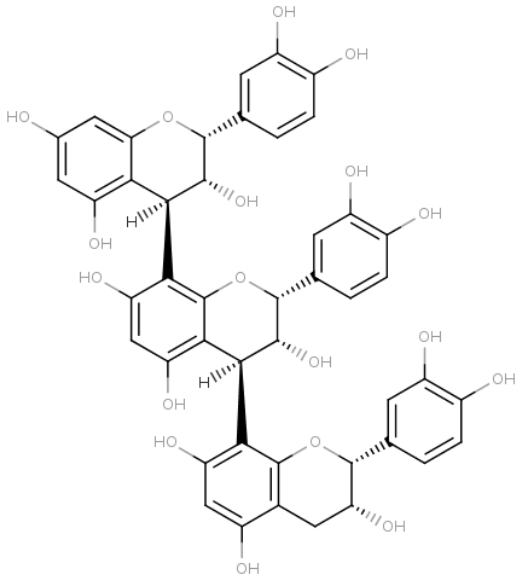
BACKGROUND





- **Epicatechin** (DP1) is absorbed in the gastrointestinal tract (GIT) and is transiently present in form of structurally related epicatechin metabolites (SREMs) in the **human circulatory system.**

- **Procyanidins** (DP2-10) with a DP > 2 have not yet been proven to be absorbed or broken down in the GIT but evidence exists that DP2-10 are catabolized by the colon's microbiome, e.g. to γ-valerolactone. **This in turn, is absorbed and further metabolized.**

Structures from: www.phenol-explorer.eu

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AIM OF THIS STUDY

The aim of this study was to investigate the contribution of procyanidins and epicatechin to cocoa flavanol intake-related improvements in vascular function in healthy volunteers

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METHODS

Study design:

Randomized, controlled, double-masked, and parallel-group dietary intervention trial

Study subjects:

45 healthy Caucasian men aged 18-35 with a BMI of 23–27 kg/m2

Subjects were screened for:

Routine clinical tests: blood pressure, electrocardiogram, blood lipids, C reactive protein, full blood count, liver enzymes, hemoglobin, glucose

Participants were randomly assigned to one of 3 groups:

2 x DP1 capsules/day for 1 month

cocoa extract containing 690 mg total flavanols (130 mg epicatechin; 560 mg proanidins)

2 x DP2-10 capsules/day for 1 month

cocoa extract containing 560 mg total flavanols (20 mg epicatechin; 540 mg procyanidins)

2 x control capsules/day for 1 month

Caffeine and theobromine content was matched to DP1 and DP2-10 capsules but all flavanols were removed

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METHODS

- **The primary endpoint** was change in flow mediated vasodilation (FMD)
- **Secondary endpoints** were plasma and urinary concentrations of structurally related epicatechin metabolites (SREMs)
- **Tertiary endpoints** included blood pressure, arterial stiffness (including pulse wave velocity), blood lipids (total, LDL and HDL cholesterol and triglycerides), as well as fasting glucose
- **Measurements** were taken before and at 2 hours after the first capsules on day 1 and before and at 2 hours after the last capsules at one month (28-30 days)

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RESULTS of Endothelial function **(FMD)**

Consumption of DP1 for one month led to a significant improvement in FMD as compared to control and DP2-10

Improvements in FMD were already seen 2 hours after consumption of the first DP1 capsules on day 1

No further improvements in FMD were seen at 1 month and 2 hours after consumption of the last DP1 capsules

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RESULTS

Structurally related epicatechin metabolites (SREMs) in plasma and urine

– Ingestion of DP1, but not DP2-10, led to a significant increase of plasma SREMs, compared to control, at 2 hours on day 1

– DP1, but not DP2-10 intake resulted in significantly higher 24h-urinary excretion of SREMs, compared to control, with no difference between day 1 and 1 month

Blood pressure & pulse wave velocity (PWV)

– Following DP1 consumption, systolic blood pressure significantly decreased at 1 month, when compared to DP2-10 and control

– A significant decrease in diastolic blood pressure was also observed 1 month after consumption of DP1 as compared to DP2-10.

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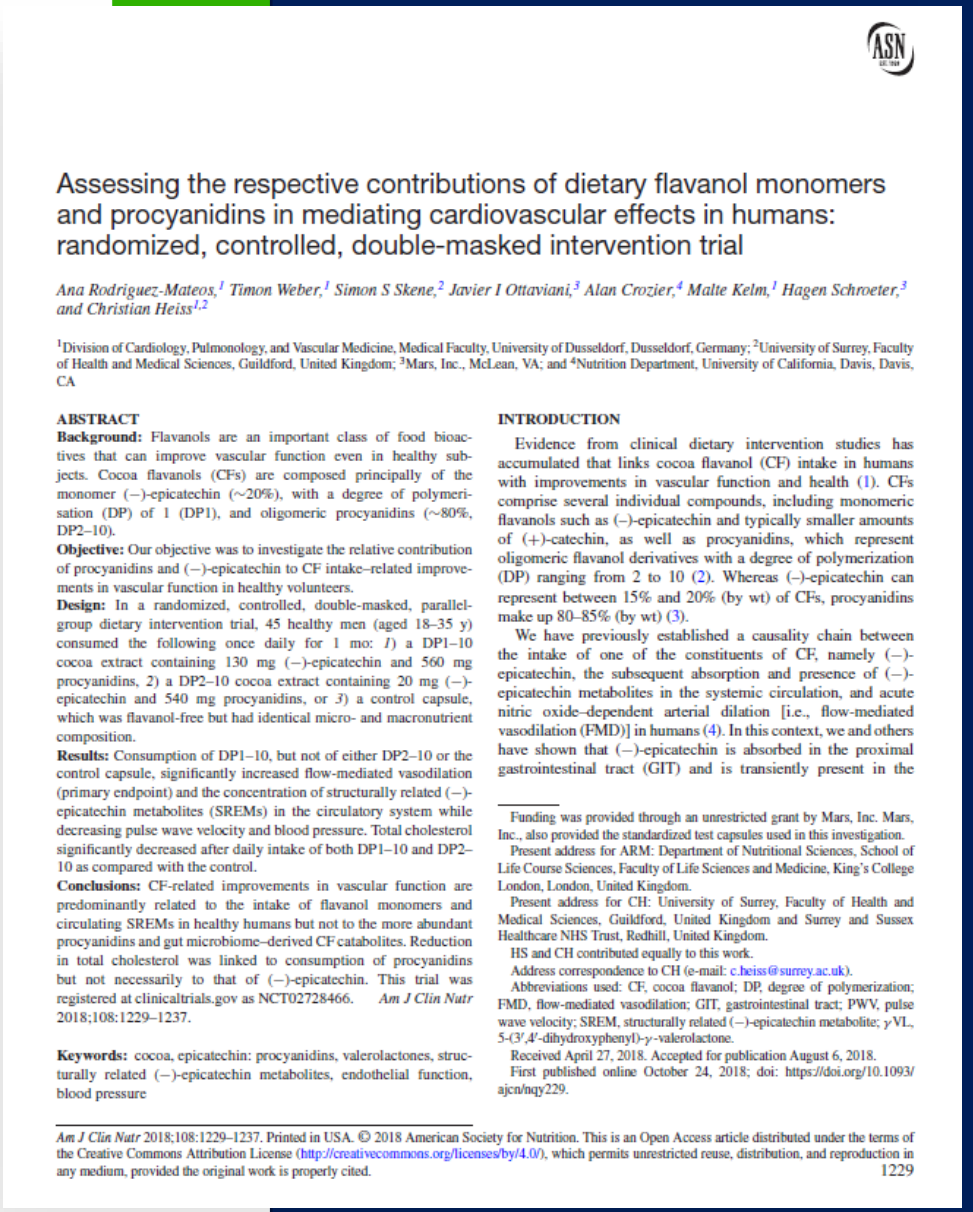
CONCLUSION

- Cacao flavanol related **improvements in vascular function are primarily** related to the intake of flavanol monomer (DP1) and circulating SREMs.
- **Reduction in total cholesterol** was linked to consumption of procyanidins (DP2-10).



Assessing the respective contributions of dietary flavanol monomers and procyanidins in mediating cardiovascular effects in humans: randomized, controlled, double-masked intervention trial

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ABSTRACT

Background: Flavanols are an important class of food bioactives that can improve vascular function even in healthy subjects. Cocoa flavanols (CFs) are composed principally of the monomer (−)-epicatechin (~20%), with a degree of polymerisation (DP) of 1 (DP1), and oligomeric procyanidins (~80%, DP2–10).

Objective: Our objective was to investigate the relative contribution of procyanidins and (−)-epicatechin to CF intake–related improvements in vascular function in healthy volunteers.

Design: In a randomized, controlled, double-masked, parallel-group dietary intervention trial, 45 healthy men (aged 18–35 y) consumed the following once daily for 1 mo: *1*) a DP1–10 cocoa extract containing 130 mg (−)-epicatechin and 560 mg procyanidins, *2*) a DP2–10 cocoa extract containing 20 mg (−)-epicatechin and 540 mg procyanidins, or *3*) a control capsule, which was flavanol-free but had identical micro- and macronutrient composition.

Results: Consumption of DP1–10, but not of either DP2–10 or the control capsule, significantly increased flow-mediated vasodilation (primary endpoint) and the concentration of structurally related (−)-epicatechin metabolites (SREMs) in the circulatory system while decreasing pulse wave velocity and blood pressure. Total cholesterol significantly decreased after daily intake of both DP1–10 and DP2–10 as compared with the control.

Conclusions: CF-related improvements in vascular function are predominantly related to the intake of flavanol monomers and circulating SREMs in healthy humans but not to the more abundant procyanidins and gut microbiome–derived CF catabolites. Reduction in total cholesterol was linked to consumption of procyanidins but not necessarily to that of (−)-epicatechin. This trial was registered at clinicaltrials.gov as NCT02728466. *Am J Clin Nutr* 2018;108:1229–1237.

Keywords: cocoa, epicatechin: procyanidins, valerolactones, structurally related (−)-epicatechin metabolites, endothelial function, blood pressure

INTRODUCTION

Evidence from clinical dietary intervention studies has accumulated that links cocoa flavanol (CF) intake in humans with improvements in vascular function and health (1). CFs comprise several individual compounds, including monomeric flavanols such as (−)-epicatechin and typically smaller amounts of (+)-catechin, as well as procyanidins, which represent oligomeric flavanol derivatives with a degree of polymerization (DP) ranging from 2 to 10 (2). Whereas (−)-epicatechin can represent between 15% and 20% (by wt) of CFs, procyanidins make up 80–85% (by wt) (3).

We have previously established a causality chain between the intake of one of the constituents of CF, namely (−)-epicatechin, the subsequent absorption and presence of (−)-epicatechin metabolites in the systemic circulation, and acute nitric oxide–dependent arterial dilation [i.e., flow-mediated vasodilation (FMD)] in humans (4). In this context, we and others have shown that (−)-epicatechin is absorbed in the proximal gastrointestinal tract (GIT) and is transiently present in the

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Abbreviations used: CF, cocoa flavanol; DP, degree of polymerization; FMD, flow-mediated vasodilation; GIT, gastrointestinal tract; PWV, pulse wave velocity; SREM, structurally related (−)-epicatechin metabolite; γVL, 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone.

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