The Road to Health Claim Success – The Cocoa Flavanols case

Dr. Stoffer Loman
NutriClaim

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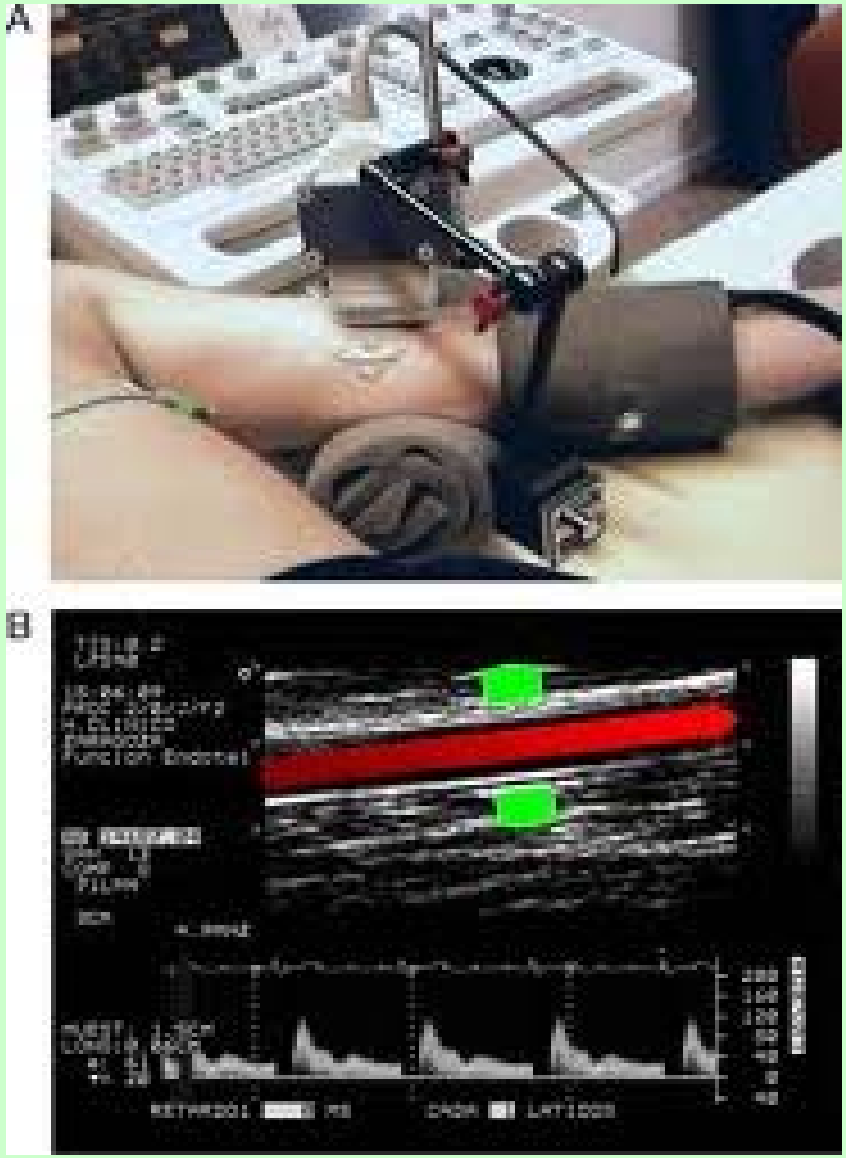
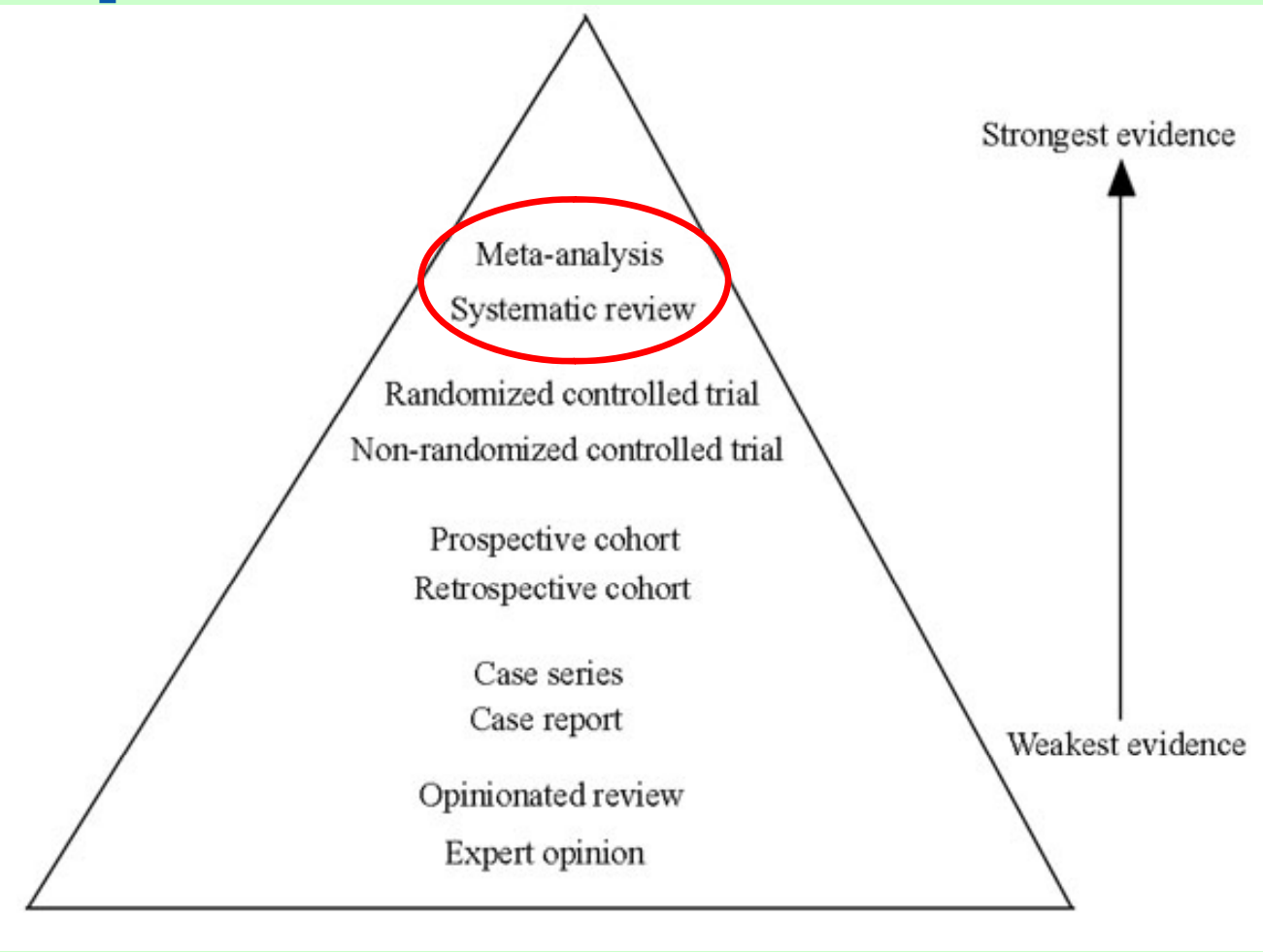
Claimed effect

Cocoa flavanols help maintain endothelium-dependent vasodilation

Flow-mediated dilation



Hierarchy of strength of evidence from peer-reviewed studies



Meta-analysis
Cocoa flavanols & ED FMD
(Hooper et al., 2012)

Selection criteria applied to determine low risk of bias:

- adequate allocation concealment
- Blinding of participants, providers, and outcome assessors
- Absence of industry funding
- study arms were similar in respect to saturated fat intake

All other trials were considered at moderate or high risk of bias.

Note: no thorough consideration of criteria that are key to EFSA

Effect cocoa/chocolate on FMD

(Hooper et al., 2012)

Meta-analyses suggested:

- acute improvement in FMD 2 h after ingestion of chocolate/cocoa
- Improvement of FMD after chronic intake

RCTs in healthy subjects

Pertinent studies selected should aim at assessing:

- Effects of cocoa flavanols on ED-FMD
- In fasting conditions
- During regular consumption (predefined as 1-12 weeks)
- Non-diseased populations

Scientific substantiation

Literature search in Pubmed:

- 25 potentially pertinent studies

Application of self-defined exclusion criteria:

- 18 studies excluded
- Further exclusion of 2 studies because of lack of control group, lack of PC and/or high drop-out rate on measurement primary endpoint

Result search and selection process:

- 5 studies considered potentially pertinent
- 1 unpublished proprietary study

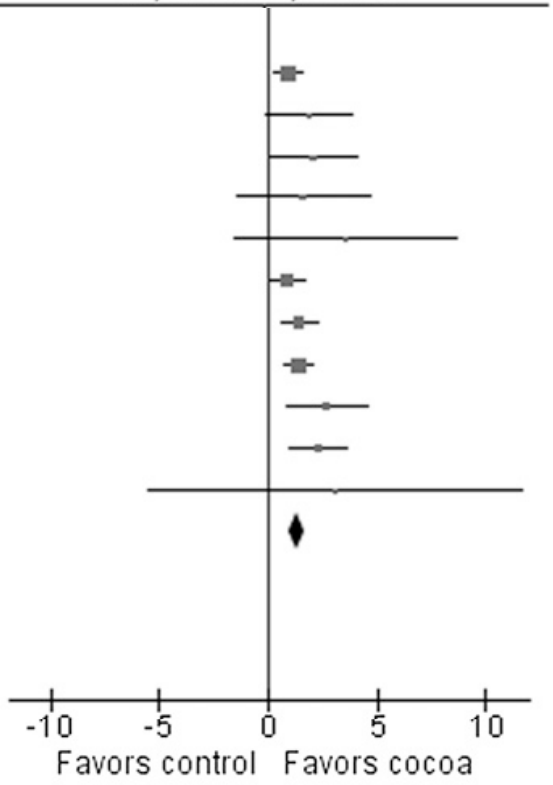
Forest plot
Hooper et al. (2012)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
2-18 weeks				
Balze[illegible]008 (38)	0.9	0.357	23.9%	0.90 [0.20, 1.60]
Davison 2008 (Ex) (41)	1.9	1.026	2.9%	1.90 [-0.11, 3.91]
Davison 2008 (noEx) (41)	2.1	1.036	2.8%	2.10 [0.07, 4.13]
Engler 2004 (43)	1.6	1.566	1.2%	1.60 [-1.47, 4.67]
Farou[illegible]e 2006 (45)	3.57	2.63	0.4%	3.57 [-1.58, 8.72]
Grassi 2005 (nBP) (49)	0.9	0.408	18.3%	0.90 [0.10, 1.70]
Grassi 2005(↑BP) (48)	1.4	0.429	16.6%	1.40 [0.56, 2.24]
Grassi 2008 (50)	1.4	0.357	23.9%	1.40 [0.70, 2.10]
Heis[illegible]010 (54)	2.7	0.94	3.5%	2.70 [0.86, 4.54]
Njike 2009 (61)	2.3	0.699	6.2%	2.30 [0.93, 3.67]
Wang-[illegible]olagruto 2006 (75)	3.1	4.383	0.2%	3.10 [-5.49, 11.69]
Subtotal (95% CI)			**100.0%**	**1.34 [1.00, 1.68]**

Heterogeneity: Tau² = 0.00; Chi² = 8.45, df = 10 (P = 0.58); I² = 0%

Test for overall effect: Z = 7.67 (P < 0.00001)

Test for subgroup differences: Chi² = 9.19, df = 1 (P = 0.002), I² = 89.1%



More studies got lost on the way! Issues

- Study design

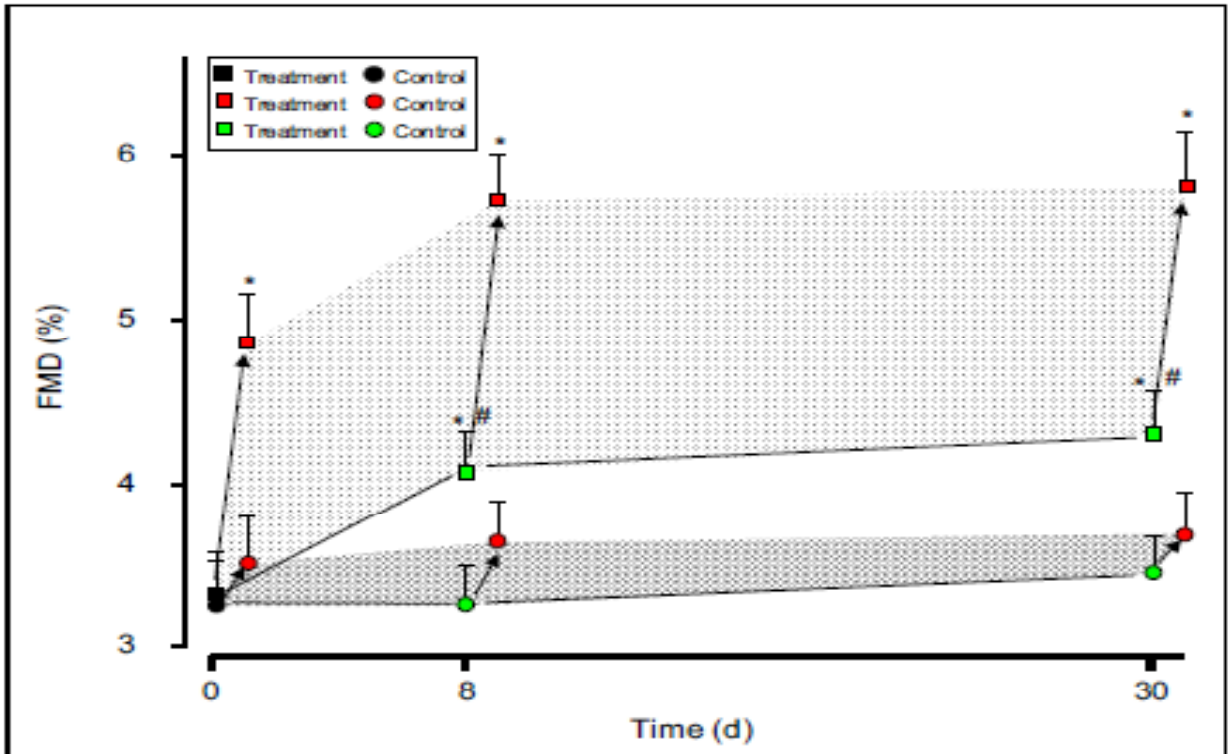


Figure 5 Acute and Sustained Effects of Flavanol-Containing Cocoa

More studies got lost on the way! More issues

Njike et al., 2011

- study appeared not to be a standalone study, but rather the continuation of a previous study (Faridi et al., 2008) on the acute effects of dark chocolate on ED-FMD

- The applicant subsequently requested that this particular study should not be considered as pertinent to the claim. The Panel agrees that no conclusions can be drawn from this study for the scientific substantiation of the claim.

More studies got lost on the way! Even more issues

- For two studies, Grassi et al. (2005/2008) EFSA noted that an effect of other food constituents in cocoa (e.g. caffeine, theobromine) on ED-FMD could not be excluded.
- White chocolate controlled
- Nevertheless, supportive

Left-over from Hooper

Of the nine studies included in the meta-analysis

ONLY

1 peer-reviewed clinical study considered pertinent!
(Davison et al., 2008)

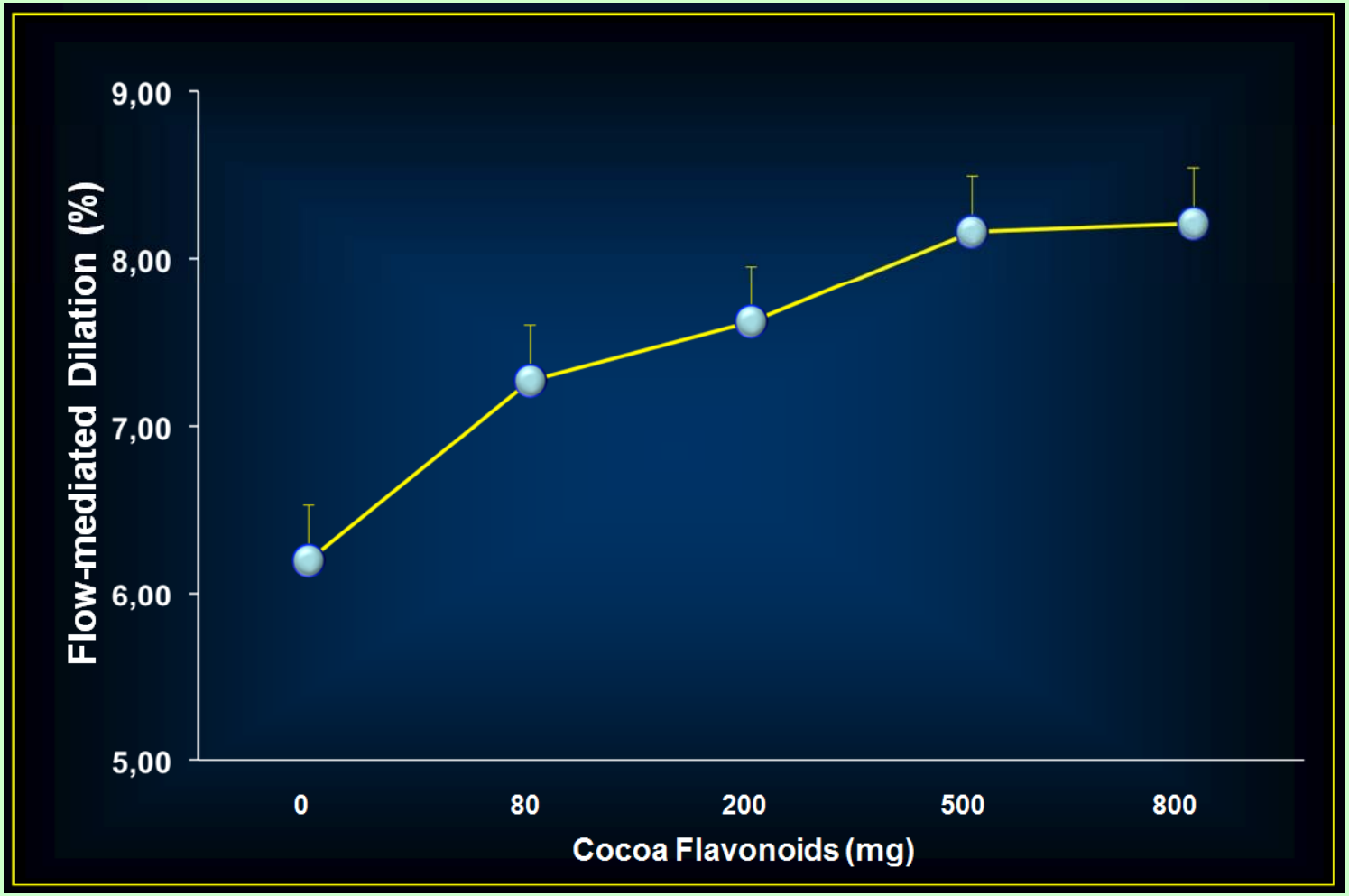
Proprietary dose-finding study

Grassi et al. (2011)

- 20 subjects (M/F)
- Cross-over (1 week intervention/1 week wash-out)
- 0 mg, 80 mg, 200 mg, 500 mg or 800 mg cocoa flavanols (monomers and oligomers, DP 1-10) in a beverage containing 10 g of cocoa powder
- ED-FMD was measured after each treatment and in fasting conditions

Dose-dependent effect

Proprietary study (Grassi et al., 2011)



Dose-dependent effect
Proprietary study

- Formal assessment of dose-response effects:
  - statistically significant when using both linear and e-power regression analyses.
- The optimum curve fit was found by using a pseudo-Hill equation, which showed a plateau.
- curve started to flatten off at approximately 200 mg cocoa flavanols per day ⟶ conditions of use!

Cause and Effect

The Panel concluded that a cause and effect relationship has been established between the consumption of 200 mg cocoa flavanols and maintenance of normal endothelium-dependent vasodilation.

Proprietary Clinical Trial indispensable

The Panel could not have reached its conclusions

without the human intervention study claimed as proprietary by the applicant

Mechanism of Action

"…. the applicant also acknowledges that the precise mechanisms involved in longer-term effects of cocoa flavanols on FMD, and their relative contribution to the effect, remain to be elucidated. The Panel notes that the evidence provided for any of these mechanisms is weak."

Authorization

Regulation 851/2013

Nutrient, substance, food or food category	Claim	Conditions of use of the claim	Conditions and/or restrictions of use of the food and/or additional statement or warning
Cocoa flavanols	Cocoa flavanols help maintain the elasticity of blood vessels, which contributes to normal blood flow (***)	Information shall be given to the consumer that the beneficial effect is obtained with a daily intake of 200 mg of cocoa flavanols. The claim can be used only for cocoa beverages (with cocoa powder) or for dark chocolate which provide at least a daily intake of 200 mg of cocoa flavanols with a degree of polymerisation 1-10	-
(***) Authorised on 24.9.2013 **restricted to the use of Barry Callebaut Belgium NV** for a period of five years.			

Cocoa flavanols and vascular elasticity

Timeline:

Application submitted:	14 December 2011
Start scientific evaluation:	20 January 2012

2 clock-stops

Opinion adopted:	27 June 2012

COMMISSION REGULATION (EU) No 851/2013 of 3 September 2013

Extension of CoU

Cocoa flavanol extract in capsules, tablets and drinks

Precedent

Water-soluble tomato concentrate (Fruitflow)

3. Scientific substantiation of the claimed effect

The Panel considers that the bioavailability of potentially active compounds in WSTC when administered as powder, tablets or capsules would not be different from that observed in other food matrices for which the health claim has been authorised (i.e., fruit juices, flavoured drinks or yogurt drinks) as long as these are easily dissolved in water.

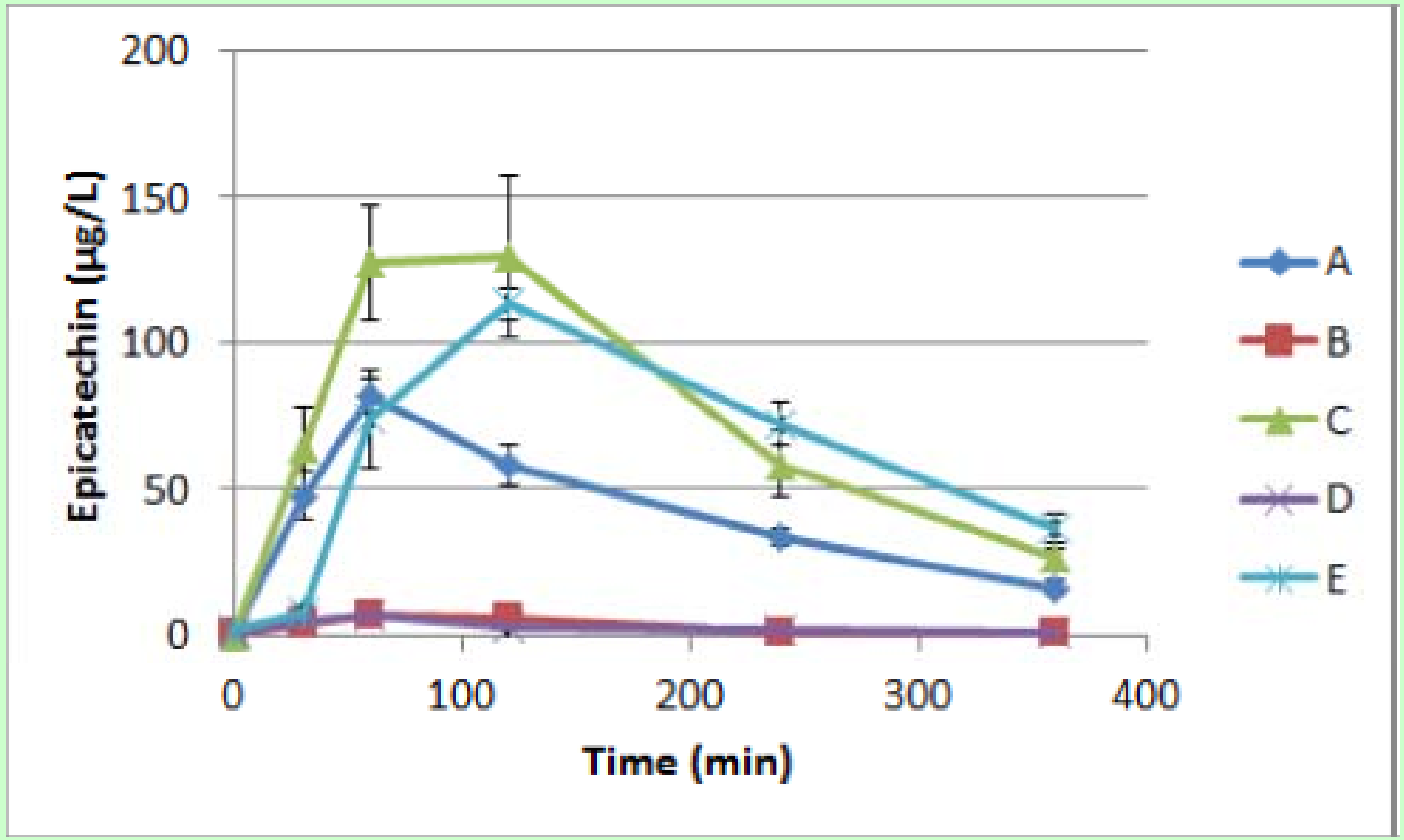
As stated in the previous assessment (EFSA, 2009) the unpublished study by O'Kennedy et al. (2007) addressed the acute effects of different forms of the tomato extract on platelet aggregation. The study

Extension CoU to cocoa flavanols

- 1 proprietary study (ProDigest, 2012)
- randomised, partially-blinded, controlled, cross-over study
- subjects – crossed-over to 5 treatments
  - High-flavanol extract in capsule
  - High-flavanol Dark chocolate
  - Low-flavanol Dark chocolate (control)
  - High-flavanol cocoa powder (beverage)
  - Low-flavanol cocoa powder (control)

  - Follow-up of epicatechin levels

Extension CoU to cocoa flavanols



Mechanism of Action

- … even if epicatechins are likely to be responsible for the acute effect of cocoa flavanols on endothelium-mediated vasodilation rather than for the long-term effect, it is unlikely that daily consumption of cocoa flavanols in the HF cocoa extract would have different long-term effects on endothelium-mediated vasodilation than cocoa flavanols in cocoa powder or dark chocolate.

Cocoa flavanols and vascular elasticity

Timeline:

Application submitted:	17 October 2013
Start scientific evaluation:	6 November 2013
1 clock-stops	
Opinion adopted:	10 April 2014
EFSA opinion released:	5 May 2014

Authorization

- Pending!


Thank you!
stoffer.loman@nutriclaim.com